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OBJECTIVE MEASUREMENT OF RELATIVE INTRACRANIAL BLOOD FLOW IN MAN

WITH OBSERVATIONS CONCERNING THE HYDRODYNAMICS OF THE CRANIOVERTEBRAL SYSTEM

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CINCINNATI

For a more complete description of the methods which have been applied to the study of cerebral blood flow the reader is referred to one of several excellent monographs on the subject.[1] Suffice it to state that none of the methods offers a means of measuring accurately the intracranial blood flow of man or animal as it exists under physiologic conditions. Many methods do, however, indicate transient qualitative changes in blood flow, and it is through the use of these procedures that much of the present knowledge concerning the physiology of the cerebral circulation has been gained. The methods which have been adapted to study of the blood flow in man are, of course, subject to the same qualification. Gibbs [2] devised a thermoelectric stromuhr which, when inserted into the internal jugular vein as it leaves the skull, accurately records qualitative changes in flow. The method is designed to record transient changes and does not give information concerning the comparative blood flow in different persons or in the same person over long periods. The use of the difference between the oxygen content of arterial and that of internal jugular venous blood, first introduced by Lennox and Gibbs [3] as an index of the rate of cerebral blood flow of man, requires the assumption that the oxygen consumption of the brain is constant.

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1. Forbes, H. S., and Wolff, H. G.: Cerebral Circulation: III. The Vasomotor Control of Cerebral Vessels, Arch. Neurol. & Psychiat. **19**:1057 (June) 1928. Wolff, H. G.: The Cerebral Circulation, Physiol. Rev. **16**:545, 1936.

2. Gibbs, F. A.: Thermoelectric Blood Flow Recorder in the Form of a Needle, Proc. Soc. Exper. Biol. & Med. **31**:141, 1933.

3. Lennox, W. G., and Gibbs, E. L.: The Blood Flow in the Brain and the Leg of Man, and the Changes Induced by Alteration of Blood Gases, J. Clin. Investigation **11**:1155, 1932.

This assumption appears valid so far as the transient effect of procedures such as carbon dioxide inhalation and hyperventilation is concerned, because the trend has been verified by the Gibbs method. In the absence of such confirmatory evidence, it is more difficult to accept the arteriovenous difference as a comparative index of cerebral blood flow, since little of a direct nature is known about the oxygen consumption of functioning cerebral tissue in normal and in abnormal states. Therefore, the final interpretation of arteriovenous differences, as an index either of blood flow or of tissue metabolism, will depend on information gained by other methods of approach.

The basic principle involved in the method to be described is similar to that used to study the blood flow to extremities by the venous occlusion plethysmographic method.[4] In the latter procedure, if the veins are sufficiently empty so that they are capable of expanding freely for a short time, sudden stoppage of the venous outflow will trap blood flowing into the veins and cause them to swell to a volume equal to that of the arterial inflow. This change in venous volume is measured by inserting the extremity into a rigid plethysmograph which is filled with water and connected with a device for recording changes in volume. The venous outflow is halted by placing a cuff around the extremity and suddenly inflating it at pressures below arterial pressure.

The bony craniovertebral covering is rigid and therefore should offer a natural plethysmograph. The cerebrospinal fluid affords a perfect noncompressible medium for transmitting changes in intracranial venous volume. If the cerebrospinal fluid is allowed to flow out of the subarachnoid space during a period when venous outflow from the cranium has been halted, then the rate of cerebrospinal fluid outflow should represent the rate of arterial inflow into the cranium.

TECHNIC

The patient is placed in the lateral recumbent position and is prepared for a routine lumbar puncture (fig. 1). After careful procainization, a sharp, short beveled needle, having an inside diameter slightly over 2 mm., a length of 8.5 cm. and a resistance to flow as illustrated in figure 2, is inserted into the lumbar subarachnoid space. An 18 gage Fremont-Smith needle is inserted one or two intervertebral spaces above, to which is attached an Ayer manometer for the purpose of observing the cerebrospinal fluid pressure. The large needle is connected with a glass reservoir, of 100 cc. capacity, partly filled with warm Ringer's solution. The cross sectional area of the reservoir is such that a volume change of 10 cc. causes the level of fluid to change only 1 cm. The level of fluid in the reservoir is adjusted so that the pressure in the entire system, including the subarachnoid space, is

4. Hewlett, A. W., and Van Zwaluwenburg, J. G.: The Rate of Blood Flow in the Arm, Heart **1**:87, 1909. Freeman, N. E.: The Effect of Temperature on the Rate of Blood Flow in the Normal and in the Sympathectomized Hand, Am. J. Physiol. **113**:384, 1935.

180 to 200 mm. above the spines of the lumbar vertebrae. The upper end of the reservoir is connected with a 20 cc. Brodie bellows by rigid rubber tubing. Volume changes in the bellows and time intervals are recorded on a revolving kymograph.

A specially devised rubber cuff, described elsewhere,[5] is fitted snugly about the neck, care being taken that it causes no obstruction to the jugular veins while deflated. The cuff is connected to a pressure bottle so that any desired pressure can be applied within it instantaneously. The effectiveness of the cuff is then tested by first closing the outflow channel and recording the response of the cerebrospinal fluid pressure to a cuff pressure of 40 mm. of mercury (544 cm. of water) and to manual bilateral jugular compression. A pressure of 40 mm. of mercury was chosen for this purpose because higher pressures cause straining and hyperpnea on the part of the patient.

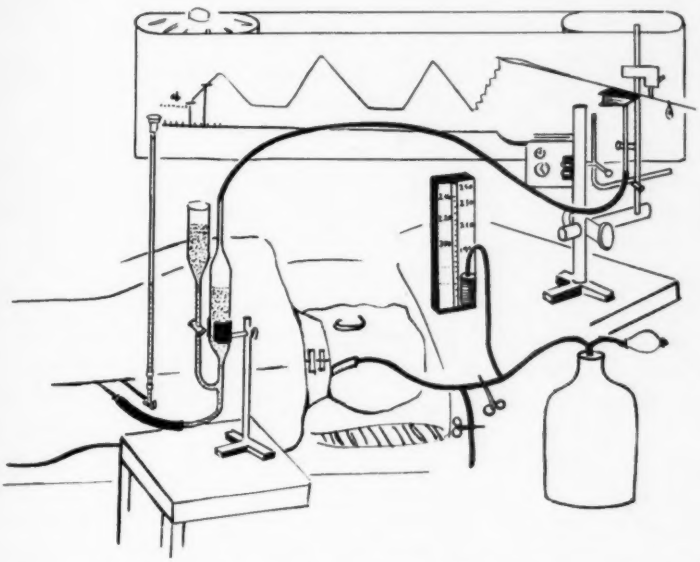

Fig. 1.—Schematic drawing of the procedure for measuring intracranial blood flow. The details are described in the text.

The outflow channel is opened, and the "blood flow" is recorded by suddenly applying a pressure of 60 to 80 mm. of mercury to the neck cuff and maintaining it until a suitable record of cerebrospinal fluid displacement is obtained, usually five to ten seconds. The cuff is then deflated, and the displaced fluid returns to the subarachnoid space, bringing the level of the bellows base line to its previous position. During the period of displacement the cerebrospinal fluid pressure is continuously observed. In this manner, as many as thirty displacement curves have been obtained in a single experiment. The bellows is calibrated by injecting into it known amounts of air and recording the change on the drum.

5. Roseman, E.; Rosenbaum, M.; Aring, C. D., and Ferris, E. B., Jr.: Cerebrospinal Fluid Dynamics in Man, Arch. Neurol. & Psychiat. **46**:72 (July) 1941.

Needless to state, aseptic technic is scrupulously adhered to throughout the procedure. The glass reservoir, needles and rubber tubing are freshly autoclaved and clean. The bellows is the only portion of the system which is not sterile, but the sterile tubing leading from the upper end of the reservoir to the bellows is 5 feet (152.4 cm.) long and is adjusted so that any fluid within would flow away from the reservoir. A commercial brand of Ringer's solution, which is sterile and free from sediment, has been used.

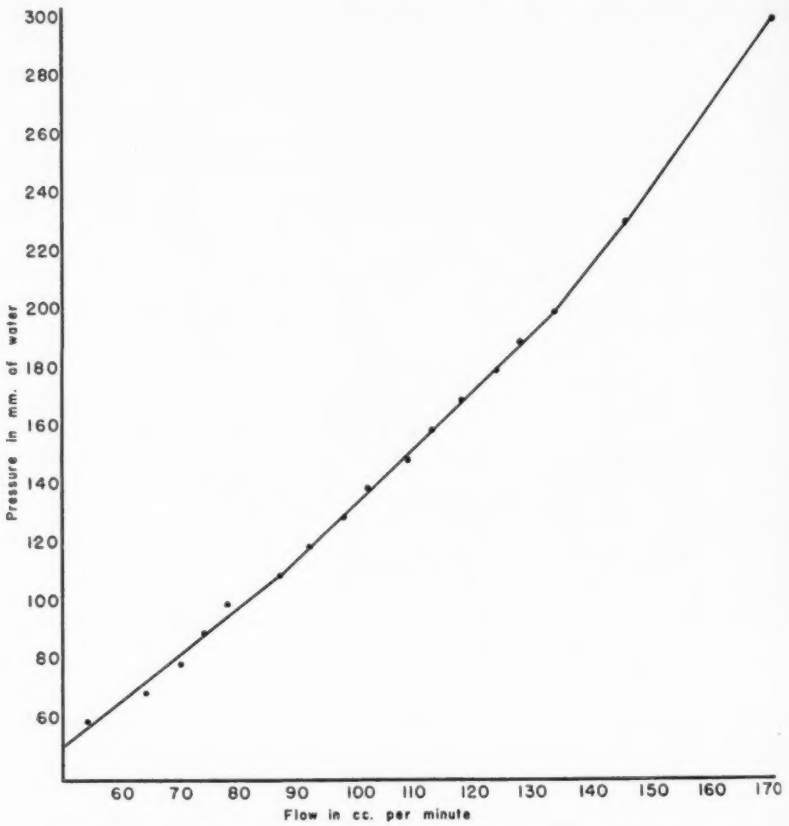

Fig. 2.—Resistance of the displacement needle to the flow of water. The curve represents the actual pressure-flow relation as obtained by means of a water model. The same needles and adapters from which this curve was obtained were used throughout these studies.

METHOD OF APPROACH

In order to gain more information concerning the accuracy of the method, various procedures, in addition to the routine already described, were carried out. The effect on the displacement rate and on the cerebrospinal fluid pressure response of varying the arbitrarily set cerebrospinal fluid pressure was determined. Simultaneous measurements of the cerebrospinal fluid and the internal jugular venous pressure at varying increments of cuff pressure were obtained under control

conditions and during transient changes of cerebral blood flow induced by hyperventilation and inhalation of carbon dioxide in order to interpret better the response of cerebrospinal fluid pressure to jugular compression. Venous pressures were measured by the direct method. The level of the spine was used as a reference point. Additional data concerning the effectiveness of the neck cuff were gained by obtaining displacement rates at varying increments of cuff pressure and during manual bilateral jugular compression. The latter procedure was routinely performed in all instances in which the cerebrospinal fluid pressure responses revealed a significant discrepancy between the pressure of the cerebrospinal fluid and that applied to the cuff (544 mm. of water). The effect on the displacement rate of procedures known to alter cerebral blood flow, including hyperventilation, inhalation of carbon dioxide, stimulation of a sensitive carotid sinus and elevation of intracranial pressure, was determined. A series of outflow rates, varying from three to thirty in number, were obtained in each of 100 successful experiments on 94 subjects. The experiment was repeated one or more times on 6 subjects and was performed on 17 "control" subjects. In addition, the hydrodynamic principles involved in the method were clarified by parallel studies on suitable water models.

EXPERIMENTAL RESULTS

Although it is evident that under proper conditions the rate of displacement of cerebrospinal fluid, carried out in the manner described, is a function of the intracranial blood flow, an understanding and control of the factors which might alter this relation are necessary in order to use the displacement rate as a comparative index of blood flow. A proper understanding of this function should also make it possible to estimate reasonably closely the actual magnitude of the volume flow of blood through the cranium. In order properly to evaluate these factors it was necessary to inquire into the following propositions: (1) that the resistance to flow of cerebrospinal fluid through the needle and apparatus remains constant throughout all experiments; (2) that the craniovertebral covering and contents (exclusive of the intracranial venous system) are sufficiently "rigid" so that an increase in intracranial venous volume will displace a similar volume of cerebrospinal fluid during the brief time required; (3) that the intracranial veins are capable of free expansion during the period of displacement; (4) that compression of the neck does not interfere with arterial blood flow into the cranium; (5) that during compression of the neck veins and displacement of cerebrospinal fluid venous blood, if it escapes from the cranium, does so in relatively constant and insignificant amounts; (6) that the rate of cerebrospinal fluid displacement is not too far removed from the physiologic intracranial blood flow, and (7) that consistent results are obtained when the method is applied to clinical study.

1. *Factor of Resistance to Flow Through the Displacement Needle.*—The basic difference between the usual plethysmographic method and the method under discussion is that in the former the opening through which the water is displaced is large and therefore offers little resistance to flow.

In the method under discussion, the size of the outflow needle is necessarily limited, and, as a result, the intracranial pressure rises during the displacement of cerebrospinal fluid into the reservoir. This rise in cerebrospinal fluid pressure, as will be shown subsequently, is due to the resistance to flow of cerebrospinal fluid through the outflow needle. The back pressure, when expressed as the height of water, is known as the friction head, or resistance head. This head was determined over the necessary range of displacement rates by measuring the volume flow of water through the outflow needle and adapter at varying heads of pressure (fig. 2). The cerebrospinal fluid resistance head, in most instances, was less than 25 per cent of the effective head of pressure applied to the neck. In order to be certain that this needle resistance factor was similar in all experiments, it was necessary to measure the level to which the cerebrospinal fluid pressure rose during the displacement. In the absence of blockage to the needle, the pressure-outflow relation in all experiments conformed closely to that shown by the curve of figure 1. Such a similarity also indicates that the resistance of the system distal to the needle (tubing, reservoir, bellows and recording lever) was negligible.

Because of the lag period inherent in the Ayer manometer, maximum cerebrospinal fluid pressure levels were not reached until five to six seconds after the beginning of a displacement curve. In order to determine whether a constant pressure-outflow relation existed throughout the entire period of displacement, a Hürthle type manometer, having a relatively short lag period, was used in 6 experiments. In these experiments the recorded pressure reached its maximum height within one-third second and remained at this level as long as the displacement rate was constant (fig. 3).

Because blockage of the outflow needle, by diminishing its mean diameter, will increase its resistance to flow, it is necessary to measure the cerebrospinal fluid pressure during some of the displacements in each experiment in order to eliminate those experiments in which blockage to the needle occurs. At any given rate of displacement, a pressure higher than that indicated by the curve of figure 2 indicates the presence of blockage. By such a procedure, the needle resistance factor is known and can be controlled throughout all experiments.

2. *Rigidity of the Craniovertebral Contents and Covering.*—The term "rigidity" is used in a broad sense to indicate the absence of volume losses, by any means, between the intracranial veins and the displacement needle during the elevation of cerebrospinal fluid pressure incident to the displacement of the fluid. The possible causes for loss of volume under such circumstances are distention of the craniovertebral covering; compression of intracranial tissue, of the cerebrospinal fluid or of the arterial system; changes in the actual volume of cerebrospinal fluid, resulting

from increased absorption or formation of cerebrospinal fluid or from leakage of cerebrospinal fluid from the subarachnoid space into the tissues, and compression of the spinal veins, since they are not distended by occlusion of the neck veins. The intracranial venous system, of course, is capable of marked change in volume, but it offers no source of error in the method, because it is this change in volume which is being recorded.

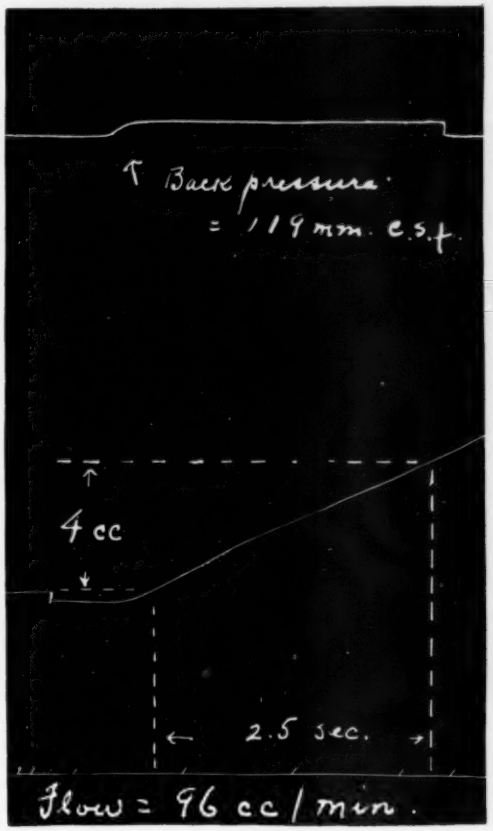

Fig. 3.—Record of the change in cerebrospinal fluid pressure which occurs during the displacement of cerebrospinal fluid by means of jugular compression. The upper line represents the cerebrospinal fluid pressure as recorded by means of a Hürthle manometer; the middle line the cerebrospinal fluid volume and the lower line the time in seconds.

The following experiment, although performed at an intracranial pressure somewhat higher than that routinely used in the method, clearly indicates that there is no significant loss in volume so far as most of the aforementioned factors are concerned. The cerebrospinal fluid pressure

was raised to 35 cm. of water, by means of elevating the reservoir, in order to compress maximally the intracranial and spinal veins. Six cubic centimeters of Ringer's solution was then injected into the subarachnoid space through the "pressure" needle at a constant rate of approximately 120 cc. per minute, and the resulting displacement through the outflow needle was recorded from the bellows (fig. 4). During the injection of 6 cc. of Ringer's solution, 5.8 cc. of cerebrospinal fluid was displaced in the same length of time. Because the pressure needle was only a short distance (two intervertebral spaces) from the outflow needle, a similar type of experiment was performed except that the fluid was injected into

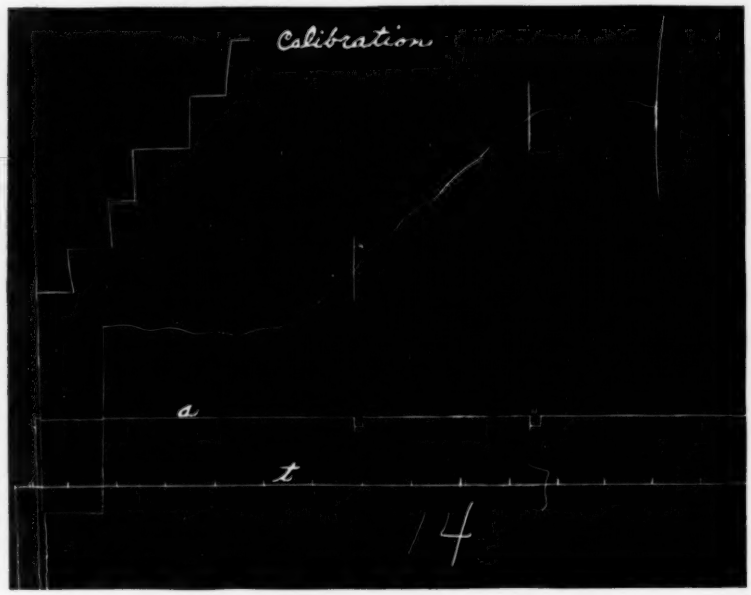

Fig. 4.—Displacement of cerebrospinal fluid during the injection of Ringer's solution into the subarachnoid space at a constant rate. The calibration of the bellows is in 2 cc. increments. The record at the upper right is the cerebrospinal fluid displacement curve; line *a* represents the signal marker and line *t* the time intervals in seconds. Between the two signal marks, 6 cc. Ringer's solution was injected into the subarachnoid space two intervertebral spaces from the displacement needle. The initial cerebrospinal fluid pressure was adjusted to 350 mm. of water in this experiment. Note the high amplitude of transmitted vascular pulsations which occurred while the pressure was elevated.

the cisterna magna. A similar close relation between injection and displacement rates was found to exist. The observation that varying the distance between the point of injection and the point of displacement did not alter this relation suggests that pressure was distributed equally throughout the craniovertebral system. The fact that 97 per cent of the

injected fluid was recovered indicates that in this experiment, in which the pressure rose from 35 to 53 cm. (at 120 cc. per minute a resistance head of 18 cm. of water develops), there was no significant loss of volume due to any of the aforementioned causes, or to any other cause which may have been overlooked.

The experiment as just described differs from the actual procedure in that the initial pressure was adjusted to a level of 350 mm. of water, while in the actual procedure it is routinely adjusted to only 200 mm. of water. Data have already been presented which demonstrate just as precisely that under the actual conditions of the procedure the craniovertebral covering and contents, exclusive of intracranial veins, do not change in volume. This is evidenced by the finding (fig. 3) that during the period of displacement the cerebrospinal fluid pressure rose to a constant level within one third of a second and remained at this level while the rate of cerebrospinal fluid displacement was constant. From the previously cited experiment, in which it was shown that the displacement of fluid was the same whether the solution was injected into the lumbar or into the cisternal region, it can be assumed that pressure is transmitted equally, and almost instantaneously, throughout the system and that the lumbar cerebrospinal fluid pressures recorded during displacement of fluid represent similar pressure levels throughout the intracranial system. Although changes in volume due to distention or compression of portions of the system may occur during the short period of displacement in which the pressure is changing from 200 mm. to its final constant level (the needle friction head), further changes in volume cannot occur as long as the pressure level is constant.[6] Since that part of the displacement curve is measured during the period of constant displacement and constant cerebrospinal fluid pressure, it is evident that the system is rigid under the conditions of the experiment. The short initial period required for the pressure to rise to a constant level probably represents, in addition to some lag in the Hürthle manometer, slight changes in volume due to compression of the spinal veins and to distention of the dural outpockets where the nerves emerge from the bony system.

In practice, the factor of leakage of cerebrospinal fluid through dural tears and through previous lumbar puncture openings must be searched for in each experiment, for such leakage frequently occurs. Often such leakage becomes evident only after a period in which the cerebrospinal fluid pressure has been raised. It can be recognized and measured either after the measurement of cerebrospinal fluid pressure responses while the displacement system is closed or after the measurement of the rate of displacement. In the former procedure, after release of the compression of the neck veins, the cerebrospinal fluid pressure falls and remains

6. This conclusion is self evident. At a constant pressure, any confined solid, liquid or gas will maintain a constant volume regardless of its elastic properties.

below its previous initial level. The amount of leakage can be determined by injecting Ringer's solution and measuring the volume necessary to return the cerebrospinal fluid pressure to its original initial level. Such leakage significantly depresses the cerebrospinal fluid pressure response to jugular compression,[5] and it is a technical factor which must be considered in evaluating cerebrospinal fluid pressure dynamics. Leakage which occurs during the displacement of cerebrospinal fluid can be determined by measuring the change in the level of the bellows base line following the procedure (fig. 5). In those experiments in which leakage does not occur and the patient remains relaxed, the level of the bellows base line and the fluid level in the reservoir may remain constant for periods up to forty minutes. Generally leakage of cerebrospinal fluid, if it occurs, has little effect on the rate of displacement. The error may be corrected, as the rate of leakage can be determined in each case.

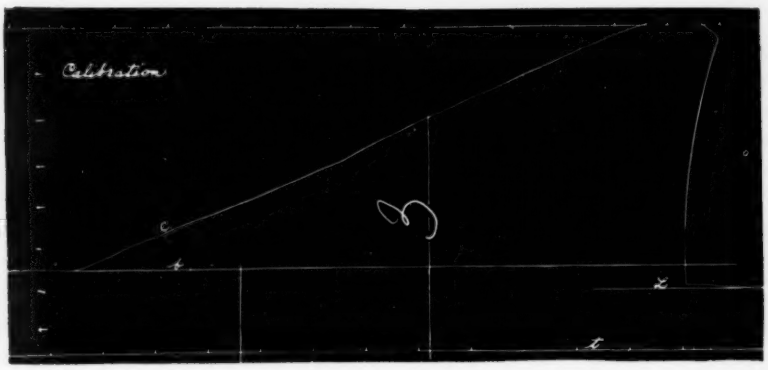

Fig. 5.—Demonstration of leakage of cerebrospinal fluid during displacement of the fluid. The lines *b* and *l* represent, respectively, the level of the bellows base line before and after the displacement of the fluid. The difference between the two levels represents the amount of leakage which occurred. Calibration is in increments of 2 cc.

3. *Distensibility of the Intracranial Veins.*—It is a well known fact that veins when in a state of partial collapse are freely distensible until they become considerably dilated. Evidence that the intracranial veins are freely distensible under the conditions of this study is the fact that the curve of the displacement rate is rectilinear and that, on testing the pressure dynamics, the cerebrospinal fluid pressure generally approaches that applied to the neck. In such a freely distensible state, then, the transfer of volume changes from within the intracranial veins to the cerebrospinal fluid should occur without loss of energy, and this factor should not become a source of error in the method.

Significant errors in the method may result, however, if the veins are initially dilated, owing to a relatively low cerebrospinal fluid pressure. The relation of low initial pressure to this factor is evidenced by the data presented in table 1, in which it is shown that in a subject having a low initial cerebrospinal fluid pressure both relatively slow displacement rates and "poor" pressure responses are enhanced simply by elevating the initial cerebrospinal fluid pressure to 200 mm. of water. It has also been repeatedly demonstrated that lowering the initial pressure by removing adequate amounts of cerebrospinal fluid will likewise depress the fluid pressure response to increased venous pressure (fig. 6). In instances in which the intracranial veins are distended, the displacement "curve" tends to be curvilinear, rather than rectilinear.

In order to be certain that the veins are in a state of partial collapse during the application of the method, the initial cerebrospinal fluid pressure is routinely adjusted to 180 to 200 mm. of cerebrospinal fluid. This

TABLE 1.—*Effect of Elevating an Initially Low Cerebrospinal Fluid Pressure on the Displacement Rate and on Cerebrospinal Fluid Pressure Dynamics in One Subject* *

	Cerebrospinal Fluid Displacement, Cc. per Min.	Cerebrospinal Fluid Pressure Response to 40 Mm. Cuff Pressure, Mm. of Water
Initial cerebrospinal fluid pressure of 50 mm. of water	36	185
Initial pressure elevated to 200 mm. of water.....	75	510

* The readings of pressure dynamics were obtained by closing the displacement needle and measuring the level to which the cerebrospinal fluid pressure rose while the pressure in the neck cuff was maintained at 40 mm. of mercury. The low initial pressure appeared to be due to dehydration in this subject.

pressure has proved satisfactory for subjects without pathologic elevations of venous pressure, and it has been ascertained that such a slight elevation of the cerebrospinal fluid pressure above the normal does not depress the displacement rate (fig. 11).

4. *Effect of Compression of the Neck Veins on Arterial Flow into the Cranium.*—That the application of external pressure to an artery does not affect the flow through it until the former exceeds the internal pressure is a well known hydrodynamic fact. Nevertheless, my associates and I have tested this point by obtaining displacement rates at varying increments of cuff pressure. Some depression of the displacement rate has occurred at pressures of 90 mm. of mercury and above, but none with pressures of 60 to 80 mm. of mercury, the range adopted for the method.

5. *Escape of Blood from the Cranium During Compression of the Neck Veins.*—It is obvious that in a given experiment the escape of blood from the cranium during various cerebrospinal fluid displacements can

be kept constant if the same occlusion pressure is utilized throughout, because the size of any channels of blood leakage will remain constant. Therefore, under such a condition, variations in the rate of cerebrospinal fluid displacement represent variations in a similar direction of the total intracranial blood flow, provided the previously mentioned technical factors are controlled.

In order to evaluate in terms of total blood flow the cerebrospinal fluid displacement rate of one subject with that of another, it is necessary

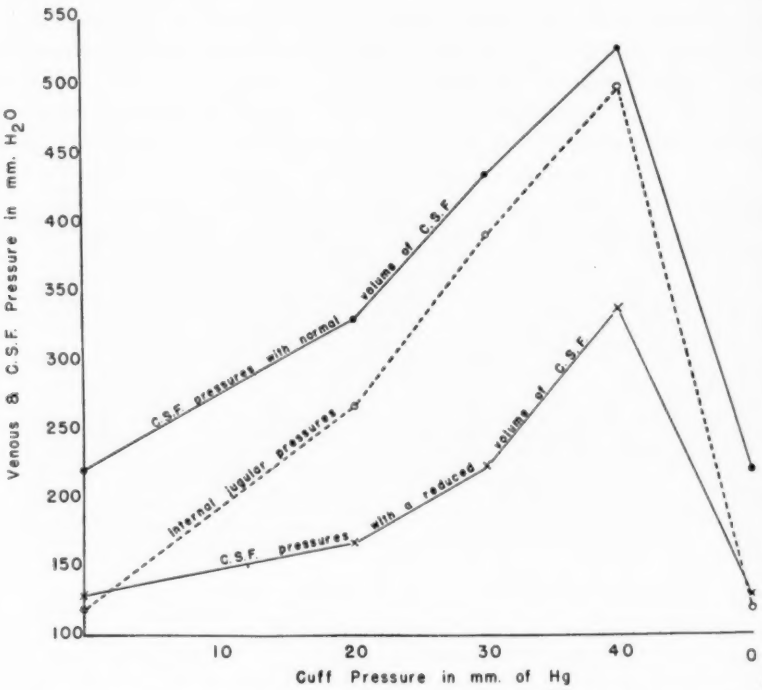

Fig. 6.—The effect, in 1 case, of removing cerebrospinal fluid on the cerebrospinal fluid pressure response to high venous pressure.

that the relative amount of blood which escapes from the cranium be essentially the same in the two subjects. Individual variations in this blood leakage factor might be due either to variations in the effectiveness of the neck cuff in compressing the deep neck veins or to variations in the size of noncompressible drainage channels (communications between the dural sinuses and the vertebral veins) relative to the size of the compressible channels (neck veins).

An attempt to evaluate the relative amount of intracranial blood which escapes during cerebrospinal fluid displacement has been made in each case by two independent methods: (1) by using in each experiment an

occlusive pressure which produces maximum displacement rates and determining in doubtful cases whether such a pressure is as effective as manual jugular compression in displacing the cerebrospinal fluid and (2) by closing the outflow needle and quantitatively measuring the response of the cerebrospinal fluid pressure to a fixed cuff pressure (40 mm. of mercury) and also to manual jugular compression.

Effectiveness of the Neck Cuff in Compressing the Deep Neck Veins: During the initial experiments, it became evident that in some cases the ordinary blood pressure cuff did not effectively compress the deep neck veins,[7] since significantly faster displacement rates could be obtained by means of bilateral manual jugular compression. In such cases, the measurement of the cerebrospinal fluid pressure responses while the outflow needle was closed demonstrated that significantly higher cerebrospinal fluid pressures could be produced by manual compression than by inflation of the cuff. A new type of cuff was therefore designed which appeared to overcome this difficulty. This cuff has been described in some detail elsewhere.[5] It was so designed that it was capable not only of considerable free inward expansion but also, when distended past this free limit, of continuing to expand significantly at increasing increments of pressure. This cuff has been used throughout these studies. It appeared to be as effective as ideal manual jugular compression, since: (1) with the outflow needle closed, the cerebrospinal fluid pressure response to inflation of the cuff paralleled the response to manual jugular compression, and (2) in all cases in which there was any doubt as to the effectiveness of the cuff, displacement rates obtained by manually compressing the neck veins never exceeded significantly those obtained by inflating the cuff.

In order further to test the effectiveness of the cuff, displacement rates were obtained at increasing increments of cuff pressure until a maximum displacement rate was obtained, and further control displacements were routinely obtained at such a cuff pressure. The cuff pressure required to obtain maximum displacement rates varied from 50 to 80 mm. of mercury. Composite values for the displacement of cerebrospinal fluid at varying increments of cuff pressure are charted in figure 7, which also shows responses to manual jugular compression. At cuff pressures above 60 mm. of mercury further increase in cuff pressure affects the displacement rate only to a slight extent (5 to 10 per cent). This shows that the maximal effectiveness of the cuff is reached at these levels and suggests that leakage through the compressed neck veins, though present, is slight under these conditions. The similarity of the curve of the group having poor cerebrospinal fluid pressure responses to that of

7. By the deep neck veins are meant the internal jugular veins and any other veins within the soft tissues of the neck which drain blood from the cranium.

the group having good pressure responses suggests that the difference in cerebrospinal fluid pressure response in the two groups was not due to ineffectiveness of the cuff.

These observations indicate clearly that the type of cuff used in these studies is an effective means of compressing the neck veins and that the effectiveness of the compression does not vary significantly from one subject to another. Such studies do not give any information concerning the relative amount of leakage of blood past noncompressible channels during the displacement of cerebrospinal fluid. These channels would include venous communications protected by the cervical vertebrae (vertebral veins) and any opening which might remain in the compressed neck veins at pressures which cause maximum displacement rates.

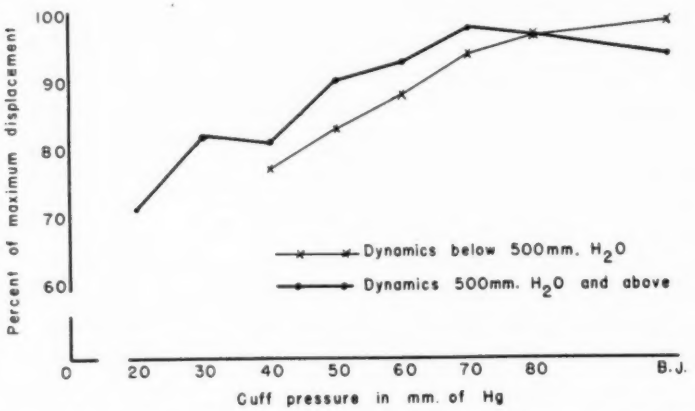

Fig. 7.—Composite curves representing the percentage of maximum cerebrospinal fluid displacement rates at varying increments of venous occlusion pressure and to manual jugular compression in 32 experiments. The patients are divided into two groups with regard to the response of their cerebrospinal fluid pressures to a venous occlusive pressure of 40 mm. of mercury (544 mm. of water).

Leakage of Intracranial Blood Through Noncompressible Channels During Compression of the Neck Veins: Information concerning the relative amount of blood which escapes through noncompressible channels can be obtained by measuring the response of the internal jugular pressure to a known pressure applied to the neck. Since it was impractical to measure the response of the jugular pressure in each subject, studies were carried out to determine whether or not the measurement of cerebrospinal fluid pressure dynamics, which was obtained in each case, would serve as an index of the jugular venous pressure. Simultaneous measurements of cerebrospinal fluid pressure and of internal jugular venous pressure were therefore carried out on 10 subjects at varying increments of

cuff pressure (fig. 8). It can be seen that the venous and the cerebrospinal fluid pressures approach each other at pressures of 40 to 50 cm. of water, the latter being slightly higher. It has already been shown that such a relation does not hold in the presence of initially distended intracranial veins or of leakage of cerebrospinal fluid. The cerebrospinal fluid pressure is considerably lower than the jugular venous pressure in these

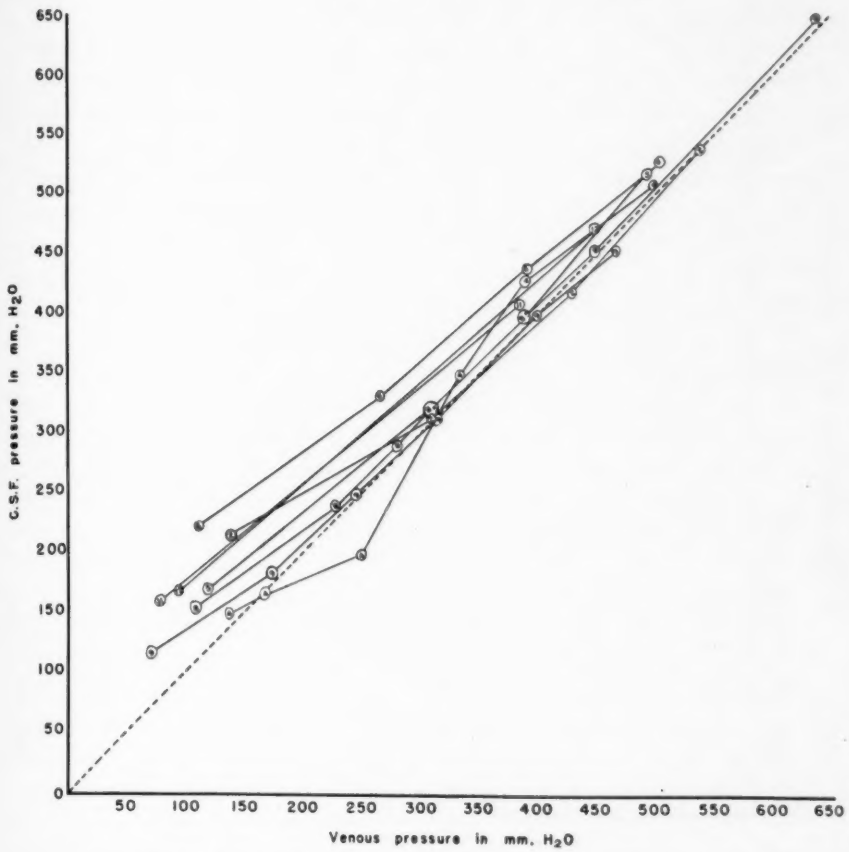

Fig. 8.—The relation of cerebrospinal fluid pressure to internal jugular venous pressure. Both pressures are referred to a common point, the cervical portion of the spine. The jugular pressure was altered by inflating the neck cuff. Note that the cerebrospinal fluid pressure is consistently higher than the venous pressure, but tends to approach it at high levels. The dotted line represents equality.

instances.[5] In the absence of such technical defects, however, fairly accurate information concerning the response of the jugular venous pressure to jugular compression can be obtained from each subject by closing the displacement needle and measuring the response of the cere-

brospinal fluid pressure to a cuff pressure of 40 mm. of mercury (544 mm. of water). This information is available for 45 subjects on whom displacement rates were also obtained (fig. 9). Instances in which leakage of cerebrospinal fluid occurred are not included in this group.

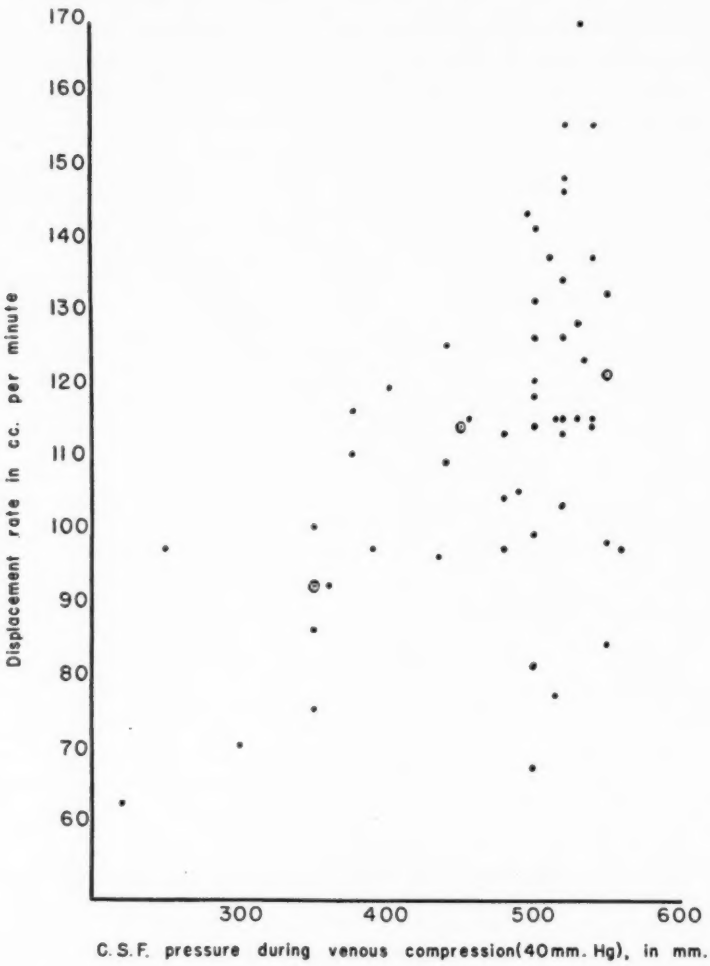

Fig. 9.—The average cerebrospinal fluid displacement rate for each of 45 subjects plotted against the response of the cerebrospinal fluid pressure (at constant volume) to a venous occlusion pressure of 40 mm. of mercury, indicated by dots. Each average was derived from three to eighteen control displacement rates. The circles enclosing dots represent the composite average of the displacement rates in subjects having a cerebrospinal fluid pressure response of 300 to 400, 400 to 500 and 500 mm. of cerebrospinal fluid and above, respectively. There is a tendency for the displacement rate to be slow in subjects having a poor cerebrospinal fluid pressure response to jugular compression. Note that the cerebrospinal fluid pressure response to 40 mm. of mercury (544 mm. of water) is above 480 mm. of water in the majority of cases.

When pressure is applied to a vein, the internal pressure will equal the external pressure so long as the vein is freely collapsible, and, for practical purposes, the pressure of the flowing blood at a point slightly upstream from the compressive force can be considered to equal the internal pressure at the point of compression. If the internal pressure falls below the external pressure it means that the vein is no longer freely collapsible, and under such a condition the venous pressure just above the constriction will depend not only on the limiting external pressure applied but also on the sectional area of any noncompressible leakage channels and on the volume flow of blood through such openings. This relation may be roughly expressed by Poiseuille's formula, $V = \frac{\pi P r^4}{8nl}$, or $P = \frac{V}{r^4} \cdot \frac{8nl}{\pi}$, in which P, the pressure head, is the difference between the pressure in the jugular vein at a point just upstream and that at a point just downstream (central venous pressure) from the constriction, V is the rate of volume flow of blood through the jugular vein, r is the mean radius of all noncompressible leakage channels, l is the distance between the above mentioned points (a constant under the experimental conditions) and n is a constant related to viscosity. Thus, it may be stated that with constant-sized noncompressible leakage channels P is directly proportional to a function of volume flow, and with a constant volume flow P is inversely proportional to a function of the mean radius of the leakage channels. During the application of an external pressure about the vein, if the central venous pressure does not change, the jugular venous pressure (at the upstream point) will vary directly with P in the preceding formula. It should again be pointed out that the aforestated relations hold only when there is some leakage of blood through noncompressible channels; otherwise, the jugular pressure would always approximate the external pressure applied.

If the cerebrospinal fluid pressure responses to a cuff pressure of 40 mm. of mercury (fig. 9) are interpreted in terms of jugular pressure responses, it is evident that in 34 cases (75 per cent) the jugular pressure rose to levels of approximately 480 mm. of water or higher, i. e., within 6 cm., or 12 per cent, of the pressure applied to the cuff. This close relation suggests not only that the cuff is effective but also that, as compared with the total blood flow, leakage of intracranial blood through noncompressible channels was insignificant in these cases. The fact that the cerebrospinal fluid pressure rarely equals the applied cuff pressure suggests, however, that some leakage of blood does take place in most instances.

Since the 25 per cent of patients having cerebrospinal fluid pressure responses below 480 mm. of water also tend to have relatively slow displacement rates (fig. 9), it is important to ascertain whether this

relation is due to a true difference in blood flow or whether it is an artefact due to the presence of relatively large leakage channels which are protected from compression. From the foregoing discussion, it is evident that at a constant high cuff pressure and a constant central venous pressure, the resulting jugular pressure is dependent principally on two variables, the relative rate of blood flow and the relative size of the leakage channels. Since there are two variables, it cannot be shown directly in each subject having a significantly diminished jugular or cerebrospinal fluid pressure response that anatomic variation in the size of the leakage channels is not the cause. However, the following evidence suggests that the poor responses are due to a relatively slow intracranial blood flow rather than to variations in the relative size of noncompressible channels.

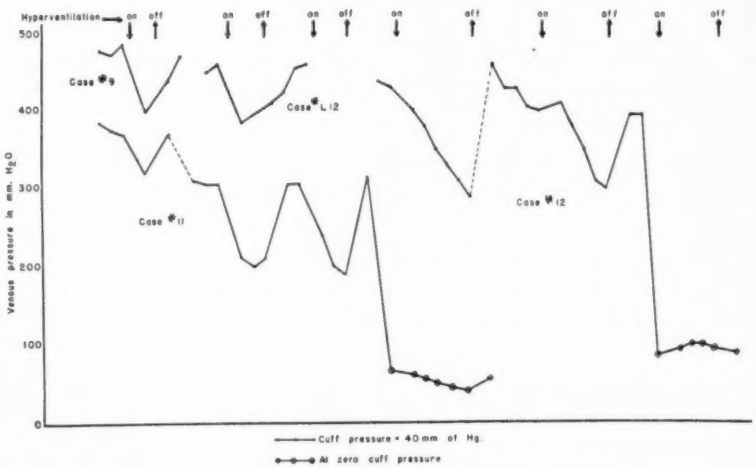

Fig. 10.—The effect of hyperventilation on internal jugular venous pressure. The solid lines connecting dots represent continuous observations on internal jugular pressure at a venous occlusion pressure of 40 mm. of mercury. The lines connecting circles represent similar observations in the absence of venous occlusion. Note the depressing effect of hyperventilation on the jugular pressure during a constant occlusion pressure.

1. In 10 experiments, the effect of hyperventilation on the internal jugular venous pressure, measured directly, was determined at a cuff pressure of zero and also at a cuff pressure of 40 mm. of mercury (fig. 10). At a cuff pressure of zero these procedures did not affect significantly the internal jugular venous pressure, indicating that the central venous pressure was not significantly altered. At an occlusive pressure of 40 mm. of mercury, hyperventilation, which is known to decrease

cerebral blood flow,[8] caused the jugular pressure to fall to levels as low as the cerebrospinal fluid pressures encountered in figure 10. Carbon dioxide inhalation, which increases cerebral blood flow,[8] caused the jugular pressure to increase in each of 3 subjects in whom it was initially low. Since in each of these subjects a constant occlusive pressure was maintained, it is evident that the size of the leakage channels was kept reasonably constant. Furthermore, it was shown that the central venous pressure was not significantly altered. Therefore, the variations in jugular pressure induced by hyperventilation and carbon dioxide inhalation were due almost solely to variations in relative intracranial blood flow. Since the levels of jugular pressure encountered during hyperventilation were just as low as the levels of cerebrospinal fluid pressure responses in the group of patients having poor responses, it is evident that such poor responses to cuff pressure may be accounted for by the presence of a relatively slow intracranial blood flow in these patients. 2. In man there are no notable communicating channels between the dural sinuses and the vertebral veins, the only vessels which are protected from compression by the neck cuff. 3. In 17 control subjects, free from cerebral circulatory disease, the response of the cerebrospinal fluid pressure to a cuff pressure of 40 mm. of mercury (544 mm. of water) ranged from 460 to 560 mm. of water and was over 480 mm. in 16, or 97 per cent. In 35 subjects suffering from acquired organic cerebral disease (dementia paralytica and cortical atrophy), the cerebrospinal fluid pressure response ranged from 300 to 550 mm. of water and was over 480 mm. of water in only 17 cases, or 48 per cent. Such a marked difference in the response of the two groups can hardly be explained on the basis of anatomic differences in the size of the communications between the vertebral veins and the cranial sinuses, since the diseases from which these patients suffered were acquired subsequent to the formation of these vessels and the cranial sinuses were not involved in the pathologic process. It would appear, therefore, that during the application of an effective cuff pressure about the neck the response of the jugular or the cerebrospinal fluid pressure is more closely related to variations in relative intracranial blood flow than to variations in the percentage of blood which escapes through noncompressible channels. Using this principle, a technic for measuring an index of blood flow which is more applicable to normal subjects than the present method is being developed.

It may be concluded, then, that the cuff is equally effective in concluding venous outflow from the cranium in all subjects and that the amount of blood which escapes from the cranium during the maximum rate of cerebrospinal fluid displacement is relatively insignificant as com-

8. Gibbs, F. A.; Gibbs, E. L., and Lennox, W. G.: Changes in Human Cerebral Blood Flow Consequent on Alterations in Blood Gases, Am. J. Physiol **111**:557, 1935.

pared with the amount of trapped blood which displaces the cerebrospinal fluid. Therefore, such displacement rates may serve as a comparative index of total intracranial blood flow in different subjects.

6. *Relation of the Displacement Rate to the Actual Rate of Intracranial Blood Flow.*—An accurate analysis of this relation has not been attempted; however, data are available which suggest that the rate of cerebrospinal fluid displacement is of the same order of magnitude as the total intracranial blood flow under physiologic conditions. Evidence has been presented which indicates that the blood leakage factor, although present, is slight as compared with the total blood flow. Except for this loss, the remaining difference is caused principally by the loss of "effective pressure head" (arterial blood pressure minus intracranial venous pressure) caused by applying the method. It has been determined in 6 cases that during the cerebrospinal fluid displacement the arterial pressure does not rise significantly; therefore any change in the effective head will be brought about chiefly by the rise in intracranial venous pressure which occurs during the displacement of cerebrospinal fluid. The leakage of intracranial blood past the cuff being assumed to be negligible, the forward flow of intracranial venous blood can be said to stop during the period of cerebrospinal fluid displacement. It has also been shown that the intracranial veins are freely distensible. Therefore, the change in the intracranial venous pressure head should be equal to the change in the cerebrospinal fluid pressure head (frictional resistance of the displacement needle), which is known for each displacement rate (fig. 2). These values are small as compared with the arterial pressure and should not influence greatly the magnitude of the blood flow. It should be pointed out that since the "cerebrospinal fluid resistance head," caused by application of the method, varies directly with the displacement rate, the percentage error due to depression of the "effective arterial pressure head" will be greater at higher displacement rates than at lower ones.

7. *Consistency of the Experimental Results.*—Clinical application of the method has shown that consistent results are obtained. In a single experiment, frequently repeated displacement rates seldom vary more than 15 per cent (table 2). Procedures which have well established effects on cerebral blood flow, such as carbon dioxide inhalation,[8] hyperventilation,[9] elevation of intracranial pressure [9] and stimulation of a sensitive carotid sinus,[10] produce changes in the displacement rate in a similar direction (figs. 11 and 12). A series of control determinations

9. Wolff, H. G., and Blumgart, H. L.: The Cerebral Circulation: VI. The Effect of Normal and Increased Intracranial Pressure on the Velocity of Intracranial Blood Flow, Arch. Neurol. & Psychiat. **21**:795 (April) 1929.

10. Ferris, E. B., Jr.; Capps, R. B., and Weiss, S.: Carotid Sinus Syncope and Its Bearing on the Mechanism of the Unconscious State and Convulsions, Medicine **14**:377, 1935.

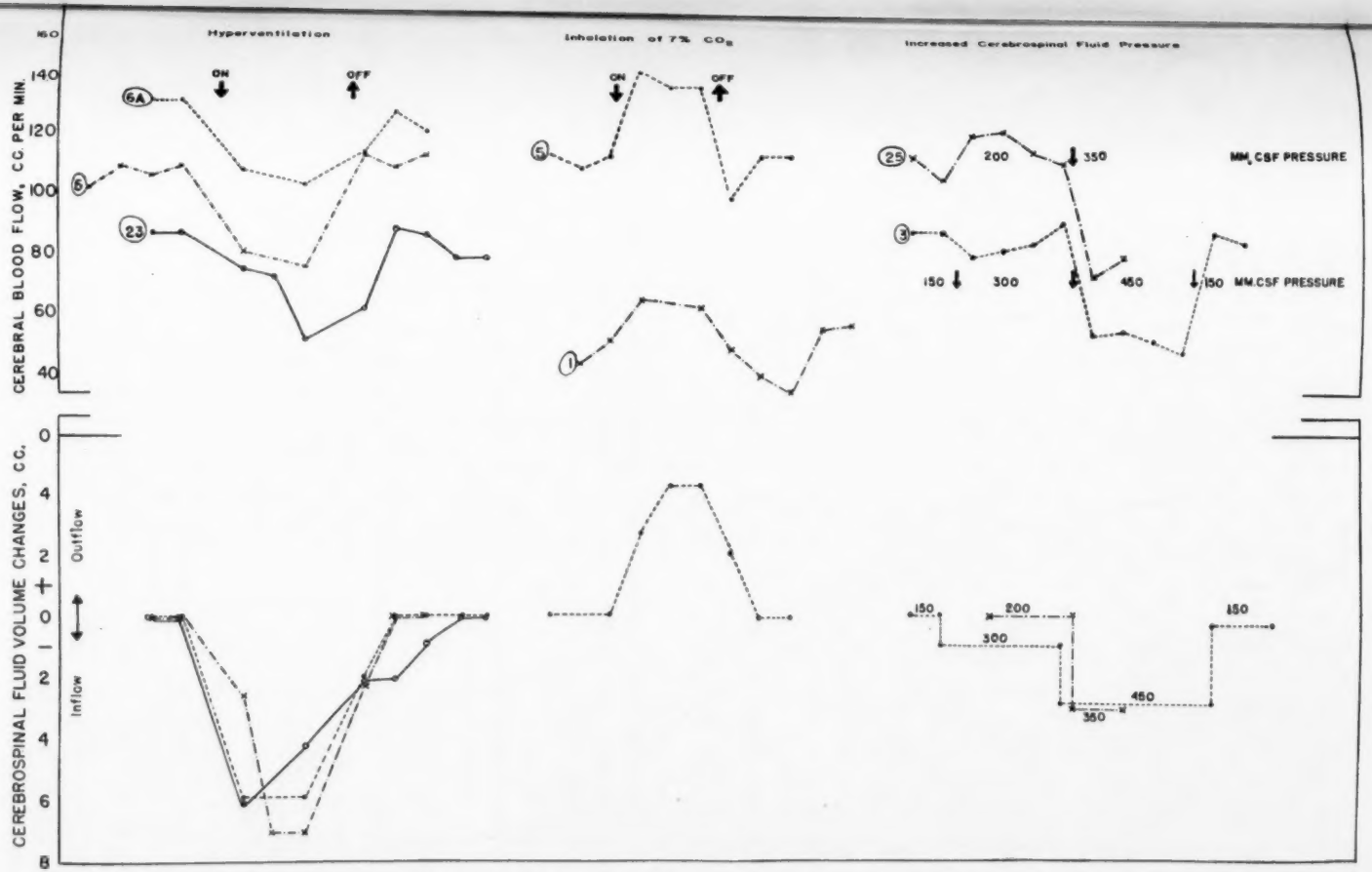

Fig. 11.—The effect of hyperventilation, inhalation of 7 per cent carbon dioxide and elevation of the cerebrospinal fluid pressure on the rate of cerebrospinal fluid displacement and the intracranial vascular volume. The upper curves represent displacement rates; the lower curves, changes in the cerebrospinal fluid volume as measured by the change in the bellows base line, and the encircled figures, the experiment numbers. The cerebrospinal fluid pressure was varied by elevating or lowering the level of the reservoir. Note that no significant change in the displacement rate occurred until the cerebrospinal fluid pressure exceeded 300 mm. of cerebrospinal fluid.

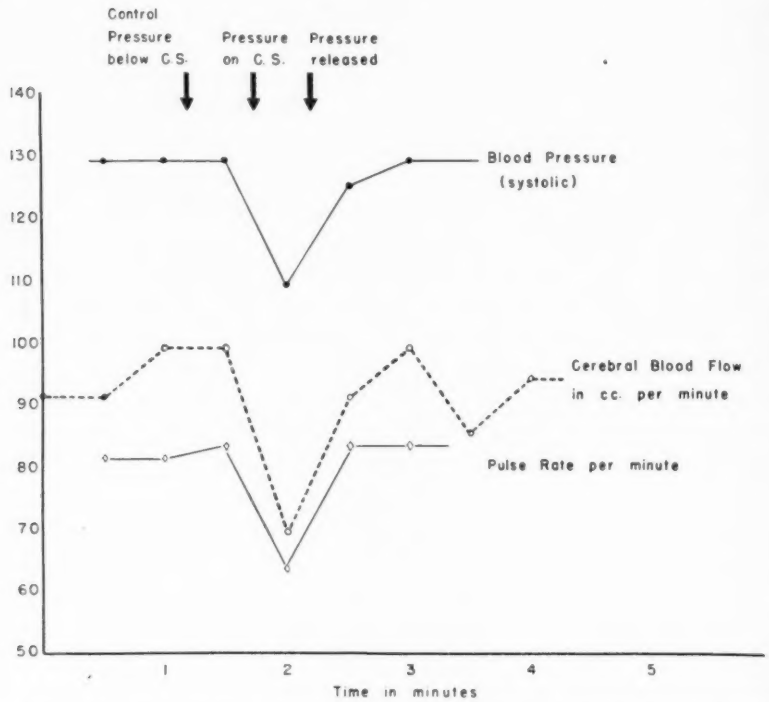

Fig. 12.—The effect of mechanically stimulating a sensitive carotid sinus on the cerebrospinal fluid displacement rate (cerebral blood flow). Blood pressure is expressed in millimeters of mercury.

TABLE 2.—*Displacement Rates Obtained on Six Subjects, Showing the Range of Variation of Control Values During a Single Experiment and on Repeating the Procedure on the Same Subject* *

No. of Experiment	Subject	Date	Consecutive Control Displacement Rates, Cc. per Min.	Average Flow, Cc. per Min.
1	J. M.	2/ 5/39	54, 50, 60, 64, 58, 63, 49, 55, 55	56
2	J. M.	2/14/39	46, 50, 40, 57, 62, 60, 59, 56, 59	54
5	C. S.	4/14/39	108, 105, 108, 112, 108, 112, 112, 112, 98, 121	110
6A	C. S.	5/11/39	107, 131, 131, 113, 127, 120, 120, 123	122
10	J. G.	5/24/39	109, 96, 92, 114, 104, 86, 86	98
13	J. G.	6/ 5/39	98, 103	101
11	M. B.	5/24/39	114, 104, 114, 120, 114, 120, 120, 114	115
14	M. B.	6/ 5/39	128, 111, 109, 109, 123, 115	116
24	M. B.	6/16/39	112, 108	110
27	A. D.	6/29/39	93, 87, 90, 98	92
28	A. D.	7/ 6/39	103, 106, 100, 100, 103, 103, 105, 109	104
45	H. R.	10/24/39	109, 112, 133, 126, 109, 109, 104	115
64	H. R.	11/21/39	96, 109, 112, 120	109

* The values for the first subject (J. M.) are not comparable with the others because a displacement needle of smaller bore was used.

has been repeated one or more times on each of 6 subjects at intervals of one to three weeks (table 2). In each subject the average displacement rate differed by less than 10 per cent. In addition, the method has been applied to a series of 17 "control" hospitalized subjects in whom there was no clinical evidence of cerebral or cardiovascular abnormalities. In this group the average displacement rate of each subject ranged from 118 to 171 cc. per minute, the composite average being 132 cc. per minute.

COMMENT

The actual procedure has caused little or no discomfort, and excellent relaxation and cooperation on the part of the subjects can be obtained. Of interest is the fact, repeatedly observed, that when measurements of pressure responses were obtained with the outflow needle closed, elevation of the cuff pressure to 50 or 60 mm. of mercury for five to ten seconds caused extreme discomfort [11] to most subjects. However, when cerebrospinal fluid was allowed to flow out, cuff pressures as high as 80 to 90 mm. of mercury applied for similar lengths of time rarely, if ever, caused any discomfort. Presumably, the marked elevation in cerebrospinal fluid pressure which occurred while the needle was closed depressed cerebral blood sufficiently to cause these particular symptoms. Headache occurred immediately in 3 subjects from whom an excessively large amount of cerebrospinal fluid was displaced during prolonged venous compression. In 1 of these subjects, replacing the fluid caused the headache to disappear promptly. In the absence of marked cerebrospinal fluid displacement headache has not been noted regardless of the height to which the cerebrospinal fluid pressure has been elevated. These observations suggest that such headaches are associated with marked changes in intracranial vascular volume, rather than with increased intracranial pressure alone.

In the 200 subjects so far tested, delayed reactions to the procedure have occurred occasionally. About 20 per cent of the subjects complained of transient headache after lumbar puncture. In 6 subjects the headache lasted for several days. In 4 subjects a severe meningeal reaction developed, consisting of fever, rigidity of the neck, elevation of the cerebrospinal fluid pressure and the appearance of leukocytes in the fluid. Cultures of the cerebrospinal fluid were sterile in each case, and the reactions subsided completely within twelve to thirty-six hours. Because of the occurrence of such reactions, studies have been limited to subjects on whom lumbar puncture was definitely indicated for diagnostic or therapeutic purposes.

11. This discomfort consisted subjectively of breathlessness and "fulness in the head" and objectively of some dyspnea and struggling.

Technically, the chief difficulty in applying the method has arisen from blockage to the flow of cerebrospinal fluid through the displacement needle. This has occurred sometimes because nerve trunks were swept against the open bevel of the needle, but more often has resulted from failure to insert the needle properly into the subarachnoid space. The incidence of failures due to blockage in 200 cases has been about 40 per cent.

Such an approach to the study of intracranial blood flow, although it entails the use of a relatively simple and well established principle, is not so simple when applied to the craniovertebral system. It has been shown clearly that variations due to technical difficulties, such as distended intracranial veins, leakage of cerebrospinal fluid through dural tears, partial blockage of the outflow needle and an ineffective cuff system, can be readily recognized and therefore controlled. Besides these technical difficulties, there appear to be only two significant factors which affect the quantitative relation between the total intracranial blood flow under physiologic conditions and the rate of cerebrospinal fluid displacement which is obtained. These factors are (1) leakage of blood from the cranium during the displacement of cerebrospinal fluid and (2) depression of blood flow due to the moderate rise in intracranial pressure which coincides with the displacement. The evidence which has been presented would indicate that the error due to these losses is slight as compared with the total blood flow and that the rate of cerebrospinal fluid displacement is of the same order of magnitude as the actual rate of blood flow. Since the displacement rates for control subjects have ranged from about 125 to 150 cc. per minute, it is probable that the total intracranial blood flow of such subjects does not exceed 250 to 400 cc. per minute.

The studies which were necessary in order to demonstrate the significance and accuracy of the method as a measurement of blood flow also add considerably to knowledge of the dynamics of the craniovertebral system of man. These observations are in agreement with the concepts generally held by neurophysiologists. From the previously mentioned evidence it is clear that the bony covering and contents of the craniovertebral cavity, exclusive of the capillary-venous system, can be considered to be rigid for most practical purposes and to conform to the Monro-Kellie doctrine. Since it has been shown that leakage of blood through noncompressible channels is slight, it also follows that most of the blood which leaves the skull passes through compressible neck veins, the chief ones being the internal jugular veins. Under normal circumstances, with the subject in a horizontal position, the cerebrospinal fluid pressure parallels, but slightly exceeds, the pressure in the internal jugular veins. The amount by which the former pressure exceeds the latter depends on the rate of blood flow through the cranium. This

relation is maintained so long as the intracranial capillary-venous system is capable of free change in volume. Factors which cause excessive distention or excessive compression of these vessels will alter the close relation which appears to exist between the intracranial venous pressure and the cerebrospinal fluid pressure.

CONCLUSIONS

A method for the objective measurement of a function of total intracranial blood flow in man has been described.

The method offers, for the first time, a means of comparing the intracranial blood flow in the same subject and in different subjects from time to time.

The values obtained appear to be of the same order of magnitude as the actual volume flow of blood through the cranium. It is estimated that the total intracranial blood flow of normal man does not exceed levels of 250 to 400 cc. per minute under the conditions of these experiments.

Observations which lead to a better understanding of the hydrodynamics of the craniovertebral system of man are presented. As a result of these data, a simpler and more applicable technic for measuring intracranial blood flow is being developed.

Drs. Jules Gelperin, Gordon Smith, Ephraim Roseman, Milton Rosenbaum, C. D. Aring and Henry Ryder; Nathaniel Brower, Ph.D., and Mrs. Jane K. Friedlander assisted in these experiments.

CORPUS STRIATUM AND THALAMUS OF A PARTIALLY DECORTICATE MONKEY

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Some of the fiber bundles associated with the corpus striatum may be studied advantageously in preparations of brains from which fibers of cortical origin have been eliminated. The brains of dogs with congenital absence of the cerebral cortex, or from which the cortex had been removed, have been studied by Holmes,[1] Edinger,[2] Morrison,[3] Papez[4] and Papez and Rundles.[5]

The corpus striatum and the thalamus in the monkey have very nearly the same structural pattern as in man, and the results of experimental work on these parts of the brain in the monkey are much more directly applicable to man than results obtained on carnivora. This paper is based on the study of a monkey (Macaca mulatta) from which a large part of the cortex of the right hemisphere had been removed by Dr. H. W. Magoun. The animal was allowed to live for ten months after the operation. After fixation in a 10 per cent concentration of formaldehyde U. S. P., a drawing was made of the left hemisphere and reversed, and

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This study was aided by a grant from the Rockefeller Foundation.

From the Institute of Neurology, Northwestern University Medical School.

The Hughlings Jackson Lecture delivered Jan. 29, 1941 at the Montreal Neurological Institute by the senior author presented the essential results of this and some other related investigations under the title "Some Experimental Studies on the Corpus Striatum."

1. Holmes, G. M.: The Nervous System of the Dog Without a Forebrain, J. Physiol. **27**:1-25, 1901.

2. Edinger, L.: Vorlesungen über den Bau der nervösen Zentralorgane, Leipzig, F. C. W. Vogel, 1911.

3. Morrison, L. R.: Anatomical Studies of the Central Nervous System of Dogs Without Forebrain or Cerebellum, Haarlem, Netherlands, de Erven F. Bohn, 1929.

4. Papez, J. W.: Thalamic Connections in a Hemidecorticate Dog, J. Comp. Neurol. **69**:103-120, 1938.

5. Papez, J. W., and Rundles, R. W.: Thalamus of a Dog Without a Hemisphere Due to a Unilateral Congenital Hydrocephalus, J. Comp. Neurol. **69**:89-102, 1938.

on this the outline of the decorticated area of the right hemisphere was superimposed to show the extent of the decortication. A photograph was also made of the right side of the brain. The part of the decorticate hemisphere which contained the corpus striatum and thalamus was embedded in pyroxylin and cut into serial sections 50 microns thick. Alternate sections were stained by the Weil method and with cresyl violet.

RESULTS

Extent of the Decortication.—Inspection of the formaldehyde-hardened brain showed that the cortex had been removed from the dorsolateral surface of the right frontal lobe and adjacent parts of the parietal and temporal lobes (fig. 1). The blood vessels had been removed with the cortex, causing softening of the subjacent white matter except for a

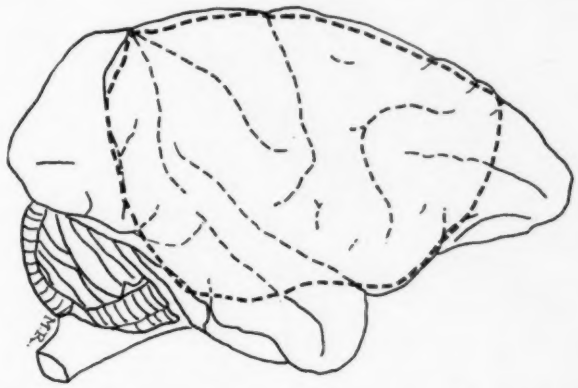

Fig. 1.—Drawing showing the area of cortex removed from the right cerebral hemisphere of a rhesus monkey.

thin layer covering the claustrum and corpus striatum.[6] Apparently all branches of the middle cerebral artery on the dorsolateral surface of the hemisphere had been removed, causing softening throughout the territory supplied by these vessels. The insula and operculums were gone, and the outlines of the corpus striatum were clearly visible on the lateral surface. The cortex on the ventral and medial aspects of the hemisphere remained, as did also that on the lateral surface of the frontal and occipital poles. It is obvious that the areas of cortex which survived were those that receive blood from the anterior and posterior cerebral arteries. The degenerated area almost reached the dorsal border of the

6. Sunderland, S.: The Production of Cortical Lesions by Devascularization of Cortical Areas, J. Anat. **73**:120-129, 1938.

hemisphere and included part of the territory supplied by the branches of the anterior cerebral artery that bend around that border onto the lateral surface,. because the actual decortication had been carried that high.

A study of the serial sections shows that the radiation of the corpus callosum to the gyri on the medial surface of the hemisphere remains intact, but no fibers from the medial cortex reach the internal capsule. The intact cortex at the frontal pole and on the ventral surface of the frontal lobe contributes many fibers to the ventral part of the anterior

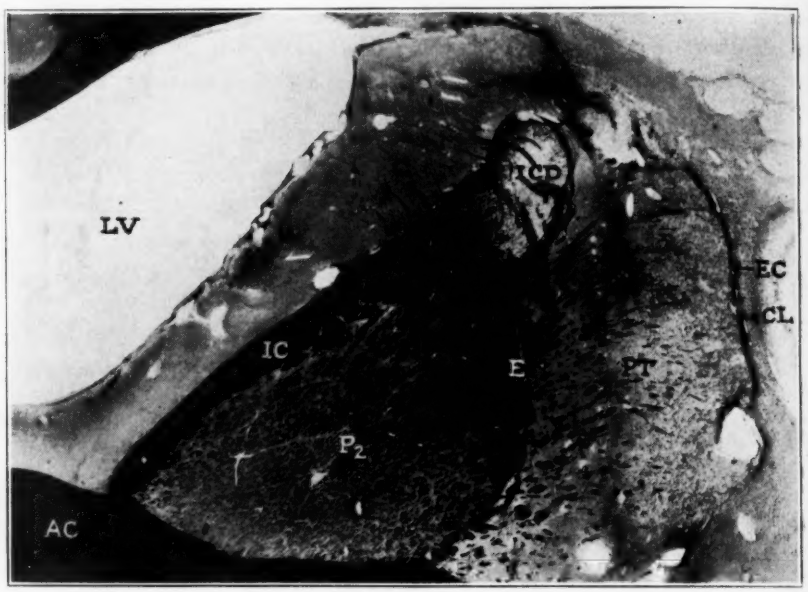

Fig. 2.—Frontal section through the decorticated hemisphere of a rhesus monkey.

In the figures the following abbreviations appear:

AC, anterior commissure; *AM*, amygdaloid nucleus; *BP*, basis pedunculi; *C*, caudate nucleus; *CL*, claustrum; *E*, external medullary lamina; *EC*, external capsule; *F*, fornix; *H*, field H of Forel; H_1, fasciculus thalamicus; H_2, fasciculus lenticularis; *HIP*, hippocampus; *I*, internal medullary lamina; *IC*, internal capsule; *ICD*, internal capsule, degenerated; *ICS*, internal capsule, strionigral fibers; *ITP*, inferior thalamic peduncle; *L*, strioluysian fibers or pallidosubthalamic fibers; *LL*, lamina limitans; *LV*, lateral ventricle; *M*, mamillary nuclei; *MT*, mamillothalamic tract; *OT*, optic tract; P_1, internal division of the globus pallidus; P_2, external division of the globus pallidus; *PH*, pallidohypothalamic tract; *PT*, putamen; *S*, strionigral fibers; $S + L$, strionigral and pallidosubthalamic fibers; *SN*, substantia nigra; *STh*, subthalamic nucleus of Luys; T_1, thalamus, nucleus anteroventralis; T_{1a}, thalamus, nucleus anteromedialis; T_{1b}, thalamus, nucleus anterodorsalis; T_2, thalamus, nucleus medialis dorsalis; T_3, thalamus, nucleus ventralis anterior; T_4, thalamus, nucleus ventralis lateralis; T_5, thalamus, nucleus lateralis dorsalis; T_8, thalamus, nucleus reticularis; *TP*, temporo-occipitopontile fibers; *ZI*, zona incerta, and *III*, third ventricle.

limb of the internal capsule. This part of the internal capsule is intact in front of the level of the anterior commissure, at which level its dorsolateral border is degenerated (fig. 2). Normal fibers from the temporal lobe lie in contact with the ventral part of the putamen and partly separate it from the part of the caudate nucleus which lies in the roof of the inferior horn of the lateral ventricle (fig. 5). The external capsule contains some normal fibers, and there are also a few on the lateral surface of the claustrum.

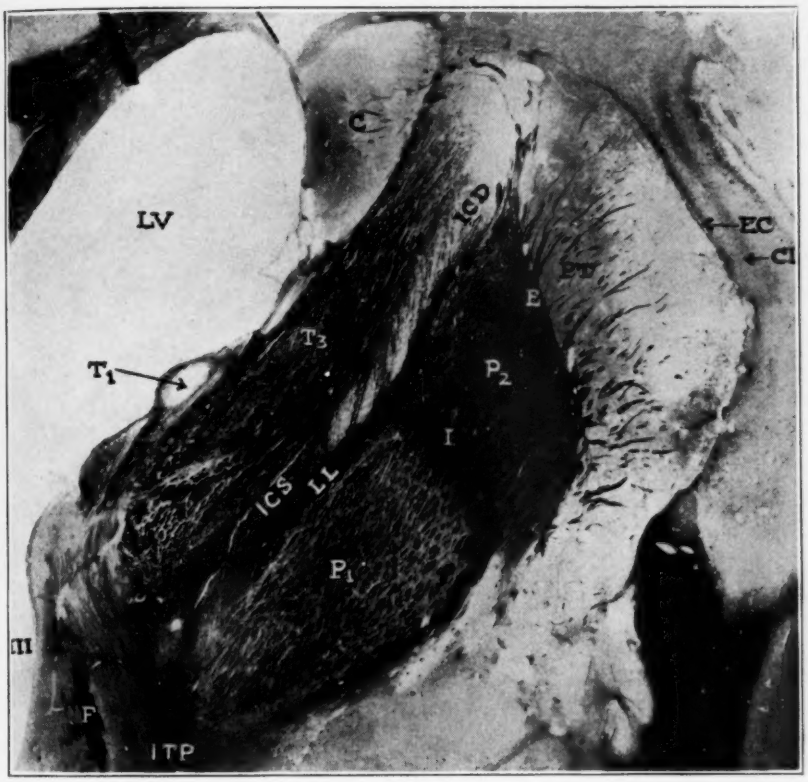

Fig. 3.—Frontal section through the decorticated hemisphere of a rhesus monkey.

The decortication extends toward the occiput at least as far as the serial sections go, namely, to a point behind the level of the thalamus where the lateral ventricle is directed downward to become the inferior horn. The insula and its operculums are gone. The cortex in the walls of the sylvian fissure is missing as far toward the occiput as our series goes, but this is not far enough to exclude the possibility that the cortex surrounding the terminal part of the sylvian fissure might have been preserved.

Basal Ganglia.—The claustrum is degenerated, and a large part of its cells have disappeared. The caudate nucleus is fairly normal except near the dorsal surface of its head, where many cells are degenerated. The ventral and medial parts of the putamen are normal, but the dorsal and lateral parts show some degeneration. These partly degenerated portions of the caudate nucleus and putamen are lightly stained in figures 2 and 3. There is no obvious decrease in the number of fibers running from the putamen into the globus pallidus, but no attempt at a quantitative determination has been made.

Fig. 4.—Frontal section through the decorticated hemisphere of a rhesus monkey.

Internal Capsule.—As shown in figure 2, the ventral part of the anterior limb is normal. It is composed of fibers joining the cortex of the frontal pole and the ventral surface of the frontal lobe with the thalamus. They enter the thalamus at the anterior end of the nucleus ventralis anterior and continue backward in that nucleus (fig. 3, T_3). In figure 2 the most dorsally placed bundles of the capsule are degenerated. These, and bundles of degenerated fibers which are added from the dorsal side as the series of sections is followed backward, enter the posterior limb of the internal capsule between the thalamus and the

lentiform nucleus (fig. 3, *ICD*). Crossing the degenerated internal capsule obliquely are bundles of normal fibers which apparently run from the nucleus ventralis anterior of the thalamus to the globus pallidus. It can be said with considerable certainty that they are not fibers from the globus pallidus to the thalamus, since in Marchi preparations of the brains of monkeys with lesions in various parts of the globus pallidus no degenerated fibers could be traced through the internal capsule to the thalamus. It will be noted that at this level the ventromedial third of

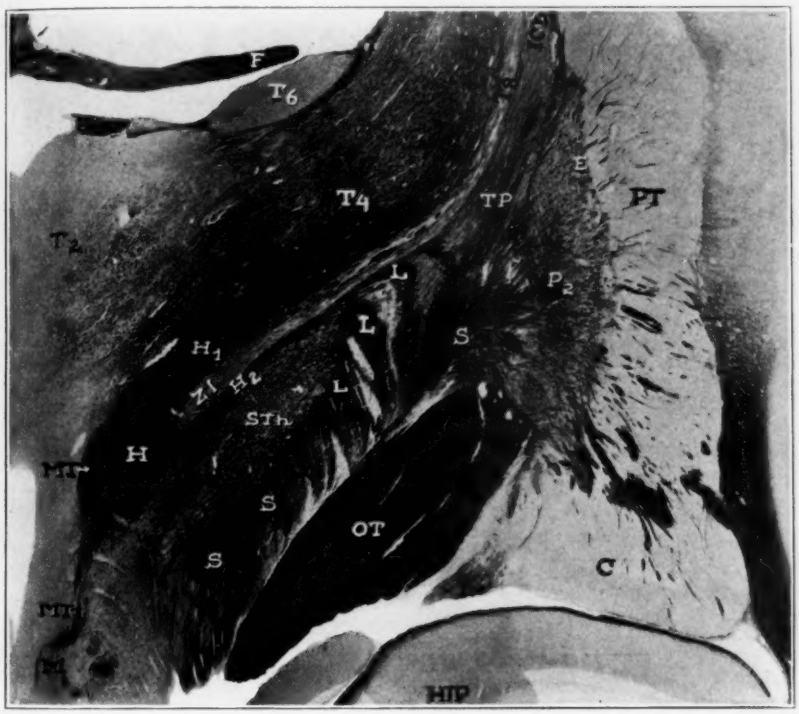

Fig. 5.—Frontal section through the decorticated hemisphere of a rhesus monkey.

the internal capsule (fig. 3, *ICS*) is not entirely degenerated, but contains many fine, lightly stained fibers, which give it much the same appearance as the lamina limitans of the globus pallidus (fig. 3, *LL*). Farther back the internal capsule contains normal fibers running in the plane of the section and belonging to the temporo-occipitopontile tract (fig. 5, *TP*).

Striopallidal Fibers.—Fibers from the caudate nucleus cross the internal capsule into the putamen and join the external medullary lamina, through which they apparently enter the globus pallidus (fig. 2). Similar fibers, in much smaller number, cross the internal capsule from the caudate nucleus into the globus pallidus. Fibers taking the latter

course have been seen in Marchi preparations of the monkey's brain after lesions in the caudate nucleus. But, surprisingly, the heavy bundles which run from the caudate nucleus into the putamen and external medullary lamina have not been seen in these Marchi preparations.[7] Most of the fibers from the putamen, those from its anterior and intermediate parts, run obliquely backward and medialward in the globus pallidus (figs. 2 to 5). A much smaller number of fibers from the most posterior part of the putamen are directed forward and medialward in the posterior extremity of the globus pallidus (fig. 6). To this extent

Fig. 6.—Frontal section through the decorticated hemisphere of a rhesus monkey.

these striopallidal fibers converge like the spokes of a wheel, and for this reason they are sometimes spoken of as radial fibers. These fibers are slender and apparently have only a thin coating of myelin. In preparations stained by the Weil method they bleach quickly during the differentiation and often assume a light brownish or grayish blue color. In Marchi preparations none of the fibers from the caudate nucleus or from

7. Ranson, S. W.; Ranson, S. W., Jr., and Ranson, M.: Fiber Connections of the Corpus Striatum as Seen in Marchi Preparations, Arch. Neurol. & Psychiat. **46**:230 (Aug.) 1941.

the putamen could be traced entirely through the globus pallidus into the ansa or the fasciculus lenticularis or into the strionigral bundles.[7]

Strionigral Fibers.—Fine fibers, having the same staining properties as the radial fibers of the globus pallidus, can be followed to the substantia nigra. Because of their small size and light brownish or grayish blue color, they can readily be distinguished from other myelinated fibers. We have been able to follow their course through the internal capsule and the basis pedunculi of normal brains of monkey and man. The position of these fibers in the capsule and the peduncle of the human brain has been described and figured by Rundles and Papez.[8] Their position in the brain of the monkey is almost exactly the same, but the

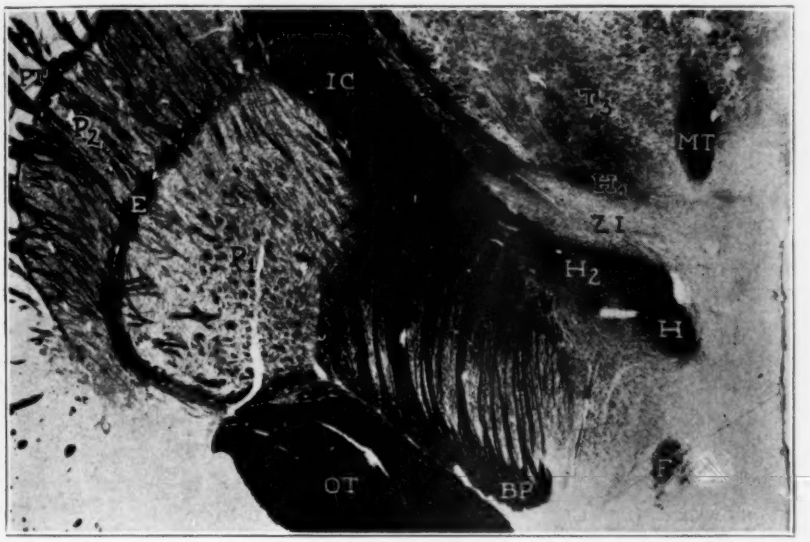

Fig. 7.—Frontal section through the brain of a normal rhesus monkey.

lateral strionigral bundles are much more prominent. In the monkey the strionigral fibers may be separated into two groups. The medial strionigral fibers can be followed from the internal capsule into the medial and intermediate parts of the basis pedunculi, within which they descend to the substantia nigra. Bundles of these fibers form lightly staining areas, which separate darkly staining areas containing fibers of cortical origin. These alternating light and dark bands give the upper part of the normal basis pedunculi the appearance of a comb (fig. 7).

8. Rundles, R. W., and Papez, J. W.: Connections Between the Striatum and the Substantia Nigra in a Human Brain, Arch. Neurol. & Psychiat. **38**:550-563 (Sept.) 1937.

In the decorticate monkey, as a result of the disappearance of fibers of cortical origin, the strionigral fibers are clearly seen in the ventromedial part of the internal capsule (fig. 3). These fine fibers closely resemble the radial fibers of the globus pallidus and the fibers which are massed in its limiting lamina. In the decorticate brain this part of the internal capsule is not separated from the limiting lamina by a distinguishable border, and one gains the impression that fibers pass from one into the other.

At the level at which the internal capsule becomes the basis pedunculi, the disappearance of fibers of cortical origin has resulted in some distortion, and the intermingling of strionigral with pallidosubthalamic fibers produces a tangle which is difficult to resolve photographically (fig. 4, $S + L$). In addition, some fibers from the globus pallidus cross the capsule in this region to enter the fasciculus lenticularis (H_2). When the preparation is examined under the microscope, it is possible to see much more than the photograph shows and the fibers of pallidal origin can be readily distinguished from the strionigral fibers. The latter are slender and pale, and are arranged in bundles which are directed ventrally as well as caudally through the region marked $S + L$ in the photograph. The pallidosubthalamic fibers and those destined to enter the fasciculus lenticularis are coarse and well myelinated and are directed medialward across this area. More medially at this same level bundles of strionigral fibers are more readily seen in the photograph (fig. 4, S). It will be obvious that while more dorsally and laterally the internal capsule is degenerated, the zone of transition between it and the basis pedunculi contains large numbers of pallidofugal and strionigral fibers. At more caudal levels the medial strionigral fibers are seen in the basis pedunculi (figs. 5 and 6, S). They can be traced into the medial and intermediate parts of the substantia nigra, and they end in its pars reticulata. Bundles of pallidosubthalamic fibers can be seen at the points marked L in figures 5 and 6. They enter into the formation of the ventrolateral capsule of the subthalamic nucleus.

The lateral strionigral fibers form a condensation in the posterior part of the globus pallidus, whence they can be traced as a good-sized bundle into the lateral part of the basis pedunculi (figs. 5 and 6, S). Like the medial strionigral fibers, these more lateral ones take a light brownish blue stain. They are closely packed together, and the bundle is so large that it stands out clearly against the surrounding parts, even in the normal brain. These fibers end in the lateral part of the pars reticularis of the substantia nigra.

Efferent Fibers of the Globus Pallidus.—The ansa lenticularis and fasciculus lenticularis and the pallidothalamic, pallidohypothalamic and pallidohabenular fibers have been described in another paper.[7] It was shown that most of the fibers which leave the globus pallidus in the ansa

and fasciculus lenticularis curve dorsally in the field H of Forel and then run laterally in the fasciculus thalamicus into the anterior part of the ventral nucleus of the thalamus. More information concerning this termination will be presented in a subsequent paragraph. The looplike course of the fibers from the fasciculus lenticularis (H_2) through field H into the thalamic fasciculus (H_1) can be traced in figures 4 and 5. That the fibers which take this course have not reached the fasciculus lenticularis from the cerebral cortex through the internal capsule, as Wilson [9] stated, is evident, for in this case the internal capsule had degenerated as the result of decortication.

As a result of the degeneration of the corticofugal fibers in the internal capsule the pallidosubthalamic fibers which cross the internal capsule at the level of its junction with the basis pedunculi are more conspicuous than in a normal brain. These fibers run medialward from the globus pallidus to the subthalamic nucleus. Because of their deep blue stain they can readily be distinguished from the paler strionigral fibers, which they cross at nearly a right angle. Although these fibers can be distinguished readily enough under the microscope, they are not sharply differentiated in the photomicrographs (figs. 4 to 6, *L*). They can be seen much more clearly in Marchi preparations after a lesion in the external division of the globus pallidus [7] and in preparations of the brain of an infant in which the internal capsule is not yet myelinated.[10]

The Thalamus.—Atrophy of the thalamus has resulted in some distortion. The nerve fibers which join the thalamus with the destroyed cortex have degenerated, and there is extensive loss of cells in many of the thalamic nuclei.

The nucleus ventralis anterior is flattened between the internal capsule and the lateral ventricle. Normal fibers of the anterior limb of the internal capsule (fig. 2) coming from the frontal pole and the ventral surface of the frontal lobe enter this nucleus at its anterior end, and at the level of figure 3 the nucleus is densely infiltrated with these fibers. What part of these fibers end in this nucleus cannot be determined. It is probable that some of them enter the nucleus medialis dorsalis, but it seems certain that the majority of them do not. It may be that some of them run backward through the anterior part of the ventral nucleus into its more caudally placed parts. The cells in the nucleus ventralis anterior are very unevenly arranged in closely packed groups, with intervening spaces devoid of cells. It seems certain that some of the cells of the nucleus have disappeared. At some points the adjacent parts of

9. Wilson, S. A. K.: An Experimental Research into the Anatomy and Physiology of the Corpus Striatum, Brain **36**:427-492, 1914.

10. Vogt, C., and Vogt, O.: Lehre der Erkrankungen des striären Systems, J. f. Psychol. u. Neurol. **25**:628-846, 1920.

the reticular nucleus seem to have suffered a comparable amount of degeneration. In cresyl violet preparations the nucleus ventralis anterior can be followed backward to the level of figure 4. Here the cells are grouped in the area within which the fibers of the thalamic fasciculus (H_1) ramify. A few of these cells can also be seen in the most medial part of the ventral nucleus in close relation to the field H_1 at the level of figure 5. This intimate topographic relation between the caudal portion of the nucleus ventralis anterior and the thalamic fasciculus suggests the probability of a functional relation. The thalamic cells are preserved throughout the territory in which the thalamic fasciculus ends. Since the nucleus ventralis anterior is differentiated from the nucleus ventralis lateralis on the basis of the preservation of the cells of the former after decortication,[11] it may be confidently asserted that the thalamic fasciculus ends in the nucleus ventralis anterior.

The cells of the nucleus ventralis lateralis and of the nucleus ventralis posterior are completely degenerated, except for a few cells in a part of the nucleus adjacent to the external geniculate body. At this level the ascending sensory fibers that terminate in the nucleus ventralis posterior are very closely grouped together, as a result of the disappearance of the intervening cells.

The nucleus medialis dorsalis is somewhat decreased in size. It does not extend backward under the habenular nucleus. Its greatest transverse measurement, taken at a point halfway between its anterior and its posterior extremity, is 28 per cent less than the corresponding measurement made on a similarly prepared section of a normal brain. The cells in the medial part of the nucleus are well preserved, but those in the lateral part have degenerated. The medial part referred to here represents more than half of the nucleus, but probably the degenerated lateral part has undergone considerable shrinkage. This twofold division of the nucleus bears no relation to the threefold division described by Walker,[11] but is in line with the division into medial and lateral parts more recently made by Walker.[12]

The centrum medianum is relatively large and apparently entirely normal.

The nucleus lateralis dorsalis (figs. 5 and 6) appears to be normal, and its cells are well preserved. The dorsal part of the nucleus lateralis posterior contains many nerve cells, but its ventral part cannot be distinguished from the degenerated nucleus ventralis posterior. The pulvinar shows degeneration of cells and increased glia in a zone extending

11. Walker, A. E.: The Primate Thalamus, Chicago, University of Chicago Press, 1938.

12. Walker, A. E.: The Medial Thalamic Nucleus: A Comparative Anatomical, Physiological and Clinical Study of the Nucleus Medialis Dorsalis Thalami, J. Comp. Neurol. **73**:87-115, 1940.

transversely across it. The dorsal part of the nucleus pulvinaris medialis is fairly normal and contains many cells. A considerable part of the nucleus pulvinaris lateralis and all of the nucleus pulvinaris inferior have a normal appearance.

COMMENT AND SUMMARY

It is well established that nuclei of the thalamus undergo degeneration when the areas of cortex to which they project their fibers are removed. On this basis the degeneration of the nucleus ventralis lateralis and the nucleus ventralis posterior was to have been expected after the removal of the cortex from the dorsolateral surface of the greater part of the hemisphere, as shown in figure 1, and the interruption of all the fibers from the internal capsule to the cortex medial to the denuded area. But it is not so easy to understand the partial degeneration of the nucleus ventralis anterior, which according to Walker [11] probably sends its fibers to the striatum rather than to the cerebral cortex. No part of the striatum was directly injured in this monkey, but the dorsal border of the caudate nucleus and the lateral border of the putamen show partial degeneration. It is possible that the degeneration in the nucleus ventralis may have resulted from this slight damage to the striatum, but one must also consider the possibility that this nucleus may send some of its fibers to the cortex. It is interesting in this connection to note that many fibers cross the degenerated internal capsule between this nucleus and the globus pallidus. Fibers from the thalamic fasciculus terminate among the surviving cells of this nucleus. Since the fibers of the thalamic fasciculus are derived from the globus pallidus by way of the fasciculus lenticularis and the field H of Forel, and since the fibers which cross the degenerated internal capsule obliquely probably arise in the nucleus ventralis anterior and end in the globus pallidus, it would seem that important reciprocal connections exist between these two structures.

It is believed that the nucleus medialis dorsalis sends its fibers to the granular layer of the cortex in the anterior part of the frontal lobe. The fact that in this case only the lateral part of this nucleus is degenerated would indicate that the intact medial part of the nucleus projects to the tip and the ventral surface of the frontal lobe, which were not decorticated. Walker [12] has recently shown that the cortex on the ventral surface of the frontal lobe receives projection fibers from the medial part of the dorsomedial nucleus.

The integrity of the nucleus of the centrum medianum is in line with the generally accepted view that it does not have cortical connections.[11]

In view of the extensive decortication, it is difficult to account for the integrity of the nucleus lateralis dorsalis and for the failure of considerable parts of the nucleus lateralis posterior and of the pulvinar to undergo degeneration. The drawing and the photograph made before the brain

was embedded indicate that all of the cortex on both sides of the fissure of Sylvius had been removed. But in view of the fact that sections were not made through the posterior part of the decorticated area, the possibility cannot be excluded that some cortex near the posterior end of the fissure of Sylvius may have been left. If this were the case it might explain the preservation of cells in the two parts of the nucleus lateralis and in the pulvinar.[11]

The pale, lightly staining fibers which join the corpus striatum with the substantia nigra, and which can be recognized by careful study of properly stained sections of the normal brain of man and the monkey, have been described and illustrated from sections of the brain of a decorticate monkey, in which these strionigral fibers have been rendered conspicuous by the degeneration of fibers of cortical origin.

Papez' [13] description of these fibers as they lie in the basis pedunculi of the monkey's brain is in full agreement with our own observations, but we cannot accept without reserve his statement that they arise in the caudate nucleus and putamen and his description of their course through the globus pallidus. Papez [4] described the strionigral fibers in a hemidecorticate dog, and Papez and Rundles [5] saw them in a dog without a cerebral hemisphere.

As far as can be judged from his various papers dealing with this subject, Papez seems to have based his opinion that these fibers arise in the caudate nucleus and putamen on two lines of evidence: 1. The fibers are similar in size and staining reaction to the striopallidal, or radial, fibers, and he expressed the belief that some of these fibers pass entirely through the globus pallidus into the strionigral bundles. 2. In a case of arteriosclerotic softening of the cortex, caudate nucleus and putamen, studied in sections stained by the Pal-Weigert method, Rundles and Papez [8] concluded that the strionigral fibers were degenerated. But had they been really degenerated it is hard to see how they could have been recognized in the basis pedunculi, in which the fibers of cortical origin were also degenerated. It seems more probable that the lightly staining strionigral fibers, which might readily be mistaken for degenerated fibers, were rendered conspicuous by the degeneration of the fibers of cortical origin.

Riese [14] had previously described fine, lightly staining fibers, which he asserted he could trace from the caudate nucleus into the stratum intermedium of the substantia nigra in Delphinus delphis, dog and man. In the dog he claimed to have followed them from the caudate nucleus in

13. Papez, J. W.: Reciprocal Connections of the Striatum and Pallidum in the Brain of Pithecus (Macacus) Rhesus, J. Comp. Neurol. **69**:329-349, 1938.

14. Riese, W.: Zur vergleichenden Anatomie der striofugalen Faserung, Anat. Anz. **57**:487-494, 1924; Beiträge zur Faseranatomie der Stammganglien, J. f. Psychol. u. Neurol. **31**:81, 1925.

Marchi preparations, but the evidence as presented is not convincing. In man he found the stratum intermedium missing in a brain with degenerated striatum (caudate nucleus and putamen).

We have seen no evidence of degeneration of these fibers in Marchi preparations of the brains of monkeys following lesions in the caudate nucleus, the putamen and the globus pallidus. But the possibility must be admitted that the degeneration of such delicate myelin sheaths might not be recognizable in Marchi preparations.[7] The question of the origin of these fibers must be left open. It is possible that they may come from the striatum or from the globus pallidus, or it may be that they take origin in the substantia nigra and end in some part of the corpus striatum. The possibility that the fibers under consideration are of cortical origin is eliminated by their presence in the internal capsule and basis pedunculi, from which fibers of cortical origin had been removed by degeneration. In spite of the uncertainty as to the source of these fibers, it seems best to continue to call them strionigral fibers unless and until it is demonstrated that this term is incompatible with their true origin and termination.

SUBCORTICAL HEMATOMA

SURGICAL TREATMENT, WITH REPORT OF EIGHT CASES

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It is the purpose of this paper to present reports of 8 cases of localized subcortical hemorrhage and to discuss this condition as a clinical entity. It will be pointed out that a clinical diagnosis can frequently be made, that the treatment should be surgical in selected cases and that the therapeutic results may be highly satisfactory.

Except in a few excellent reports, which will be cited later in this paper, intracerebral hemorrhage has long been assumed to fall into one of two categories: the multiple petechial hemorrhages resulting from trauma (Munro,[1] Martland and Beling,[2] Gross and Ehrlich,[3] Cassasa,[4] Winkelman and Eckel,[5] Shapiro and Jackson [6]) and the spontaneous hemorrhages of apoplexy, usually occurring deep in the internal capsule (Robinson,[7] Sachs,[8] Spiller,[9] Tisell [10]). The solitary hematomas lying close beneath the cortex, whether traumatic or spontaneous, have received surprisingly little attention.

REPORT OF CASES

Traumatic Hemorrhage.—In the first 2 cases trauma was unquestionably responsible for the hemorrhage, and in the third trauma was

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From the Department of Surgery, Vanderbilt University School of Medicine.

1. Munro, D.: Craniocerebral Injuries, New York, Oxford University Press, 1938.
2. Martland, H. S., and Beling, C. C.: Traumatic Cerebral Hemorrhage, Arch. Neurol. & Psychiat. **22**:1001 (Nov.) 1929.
3. Gross, S. W., and Ehrlich, W.: Diagnosis and Treatment of Head Injuries, New York, Paul B. Hoeber, Inc., 1940.
4. Cassasa, C.: Multiple Traumatic Cerebral Hemorrhages, Proc. New York Path. Soc. **24**:101, 1924.
5. Winkelman, N. W., and Eckel, J. L.: Brain Trauma: Histopathology During Early Stages, Arch. Neurol. & Psychiat. **31**:956 (May) 1934.
6. Shapiro, P., and Jackson, H.: Swelling of the Brain in Cases of Injury to the Head, Arch. Surg. **38**:443 (March) 1939.
7. Robinson, G. W., Jr.: Encapsulated Brain Hemorrhages: A Study of Their Frequency and Pathology, Arch. Neurol. & Psychiat. **27**:1441 (June) 1932.
8. Sachs, B.: Apoplexy, Bull. New York Acad. Med. **4**:1250, 1928.
9. Spiller, W. G.: The Duration of Life After Extensive Hemorrhage of the Brain, J. A. M. A. **51**:2101 (Dec. 19) 1908.
10. Tisell, F.: Comparative Clinical Study of Apoplectic Cerebral Hemorrhage and Softening of the Brain, Hygiea **94**:934, 1932.

probably the etiologic agent. The 3 cases represent the early (acute), the intermediate (subacute) and the late (chronic) stage, in the order in which they are presented.

CASE 1 (referred by Dr. W. O. Vaughan, Nashville, Tenn.).—G. LeB., aged 5 years, fell 5 feet (152 cm.), striking the back of his head on a concrete floor, twenty hours before admission. He was not rendered unconscious, but went home and slept for two hours. He then awakened, seemed alert and was taken to see a motion picture. There he complained of headache, and, when taken home, slept for four hours. When he awakened, he vomited projectilely. The next morning he was more drowsy, but talked normally when aroused. He was admitted to the pediatric service and was found to have weakness of the right side of the face and a positive Babinski sign on the right. Roentgenograms of the skull showed no fracture.

The following morning he was difficult to arouse, his spinal fluid was found to be blood tinged and he was seen in neurosurgical consultation. Examination showed a stiff neck, early choking of the disk, motor aphasia, right hemiplegia, most marked in the face, and a Babinski sign bilaterally. The blood pressure was 120 mm. of mercury systolic and 80 mm. diastolic.

Operation (Sept. 10, 1937).—A single burr hole was made in the left temporal region. There was no extradural or subdural hemorrhage. A blunt ventricular needle inserted into the brain entered a cavity 3 cm. beneath the cortex, from which was evacuated a large amount of viscid, chocolate brown fluid, undoubtedly liquefied blood clot. The wound was then closed, although it was realized that removal of any solid clot which remained might become necessary.

However, he improved rapidly, and the only other procedure employed was evacuation of a small additional amount of liquefied clot by puncture between the edges of the skin on the second postoperative day. The hemiplegia disappeared rapidly; speech returned by the fifth postoperative day, and he was discharged on the seventh day, free of symptoms. There have been no further symptoms up to the present.

CASE 2 (referred by Dr. Jesse Smith, Gamaliel, Ky.).—O. B., a 16 year old white boy, was struck on the left side of the head by a stone nine days before admission. He was unconscious for five minutes. Subsequently, he was able to walk home, but it was observed that "he got his words mixed up" in speaking. He vomited several times and was drowsy for two days. Speech grew more difficult, and, two days before admission, the right side of his face began to twitch frequently.

A large depressed fracture was palpable and demonstrable roentgenographically in the left lower parietal region. The boy was alert, but understood only the simplest phrases and could say only a few incoherent words. He could not write but could understand very simple written requests. He seemed to have right homonymous hemianopia, but careful perimetric measurement was impossible. The optic disks were normal. Sensation was slightly diminished and motor power greatly impaired on the right side of the face. There was moderate weakness of the extremities on the right, but no spasticity, clonus or Babinski sign.

Operation (Sept. 20, 1933).—The fracture was badly comminuted, and the depressed bone was removed, an area of dura about 5 cm. in diameter being exposed. Surprisingly, the dura was intact, and its appearance was normal. There was no subdural hemorrhage, but the cortex was contused and discolored. In the second postcentral convolution was a dark purple, fluctuant area. This was

incised, and a large amount of dark, semisolid clot extruded. The large subcortical cavity was evacuated by suction. No membrane was present.

The patient made a rapid, complete and uneventful recovery and has remained entirely free of symptoms.

CASE 3 (referred by Dr. E. B. Van Ness, Gulfport, Miss.).—G. R., a 25 year old electrician, had three generalized convulsions in the four months prior to admission. There were no known focal features in the attacks and no residual symptoms. At the age of 6 he had fallen on his head and was said to have had a fractured skull. Details of this accident were lacking. There had been no other injuries, diseases or symptoms referable to the nervous system. Dr. Van Ness discovered an area of flocculent calcification in the right occipitoparietal region (fig. 1 *A*).

Operation (March 1, 1937).—After reflection of an osteoplastic flap over the calcified area, the dura was found slightly adherent to the cortex. Underlying this was a contracted, hard mass lying in the brain. Its surface showed brownish

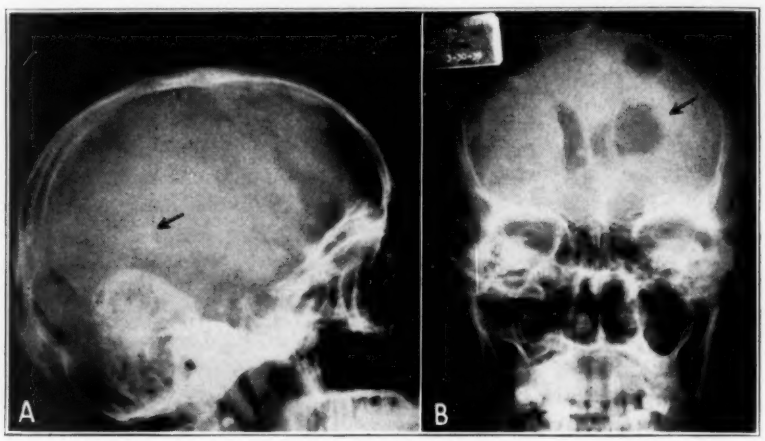

Fig. 1.—Roentgenograms. In *A* (case 3) the old, thick hematoma wall is partly calcified. This was the only basis for localization in this case. In *B* (case 8) the cyst (arrow), as well as the ventricles, has been injected with air.

discoloration, and the irregular area of calcification was palpable. The mass was excised, after frozen section had shown only cicatricial tissue.

Except for a postoperative, extradural clot, which necessitated reopening the wound, recovery was satisfactory. In the four years since operation, the patient has had two fleeting "blank spells," but no major convulsions.

Microscopic study showed a cicatrix containing heavy calcium deposits. There was no evidence of neoplasm (fig. 3 *B*).

Although there is no proved relation of the mass to the childhood injury, it seems likely that a solitary hematoma was gradually organized and calcified in the intervening nineteen years.

Spontaneous Hemorrhage.—In the following 4 cases no injury had occurred. These cases also are presented in the order of increasing duration of symptoms.

CASE 4 (referred by Dr. David Strayhorn, Nashville, Tenn.).—K. M., a 19 year old army recruit, who had previously been entirely healthy, was peeling potatoes on "kitchen police" duty when he complained that his left arm and left side of his face "felt funny." He walked with a limp and seemed "groggy." He was admitted to the hospital within three hours of the onset. The blood pressure was 130 mm. systolic and 85 mm. diastolic. He was drowsy but rational; there was left hemiparesis, more marked in the face and arm than in the leg. The cerebrospinal fluid was blood tinged, but its pressure was only 120 mm. of water. His condition remained unchanged for two days, when he had a convulsion, the hemiplegia became complete, he lapsed into deep coma and the blood pressure rose to 168 mm. systolic and 70 mm. diastolic and the cerebrospinal fluid pressure to 500 mm. of water.

Operation (Sept. 20, 1940).—A burr hole was made in the right temporal region. No extradural or subdural clot was encountered. A ventricular cannula entered a hemorrhagic cavity 3 cm. beneath the cortex, and a large quantity of old, dark blood escaped. A large subtemporal opening was made in the bone; the dura was opened and the cortex incised. A considerable additional amount of semisolid and liquid blood was removed by suction. No origin of the bleeding could be found in the cavity.

The patient recovered slowly but steadily and was discharged to an army hospital for convalescence on October 16. A report from his medical officer on November 13 stated that he was improving steadily.

CASE 5 (referred by Dr. Ben Burdette, Shelbyville, Tenn.).—Mrs. N. T., aged 38, had a "stroke" nine months before admission. Her right hand suddenly felt numb, and thirty minutes later she lost consciousness for twelve hours. When she was aroused, the right extremities were paralyzed and numb and she was unable to speak. Recovery began promptly, but was limited in degree, and marked weakness of the right side and difficulty in speech persisted. Six months after the "stroke" she had the first of three jacksonian convulsions, beginning in the right hand.

On admission, she had partial global aphasia, with complete alexia, spastic right hemiparesis and hemihypesthesia with complete astereognosis. The Hoffmann sign was positive, and there was marked reflex grasping on the right. There were no signs of increased pressure. Examination of the cerebrospinal fluid and roentgenograms of the skull gave normal results.

Operation (Oct. 14, 1937).—Left osteoplastic craniotomy was performed. When the dura was opened, a soft, discolored area was seen in the second parietal convolution. This was incised, opening a cyst, 3 cm. in diameter, which contained characteristic yellowish brown fluid. The cyst wall stripped away easily and was removed in one piece.

The patient recovered rapidly and was discharged on the twelfth postoperative day. Within a few weeks the weakness on the right had disappeared and the aphasia was almost gone. Her physician reports that she has had no further symptoms.

CASE 6 (referred by Dr. T. A. Whitfield, Nashville, Tenn.).—S. R., a man aged 27, was admitted eleven months after a sudden attack of aching pain and numbness in the left arm and hand, which lasted about one week and disappeared, with no residual symptoms except occasional headache. Seven months later, after a playful scuffle (without trauma to the head), he suddenly vomited, became violently dizzy and staggered to the left. Again the symptoms disappeared in a few days, except for headaches. Similar attacks occurred two months and two

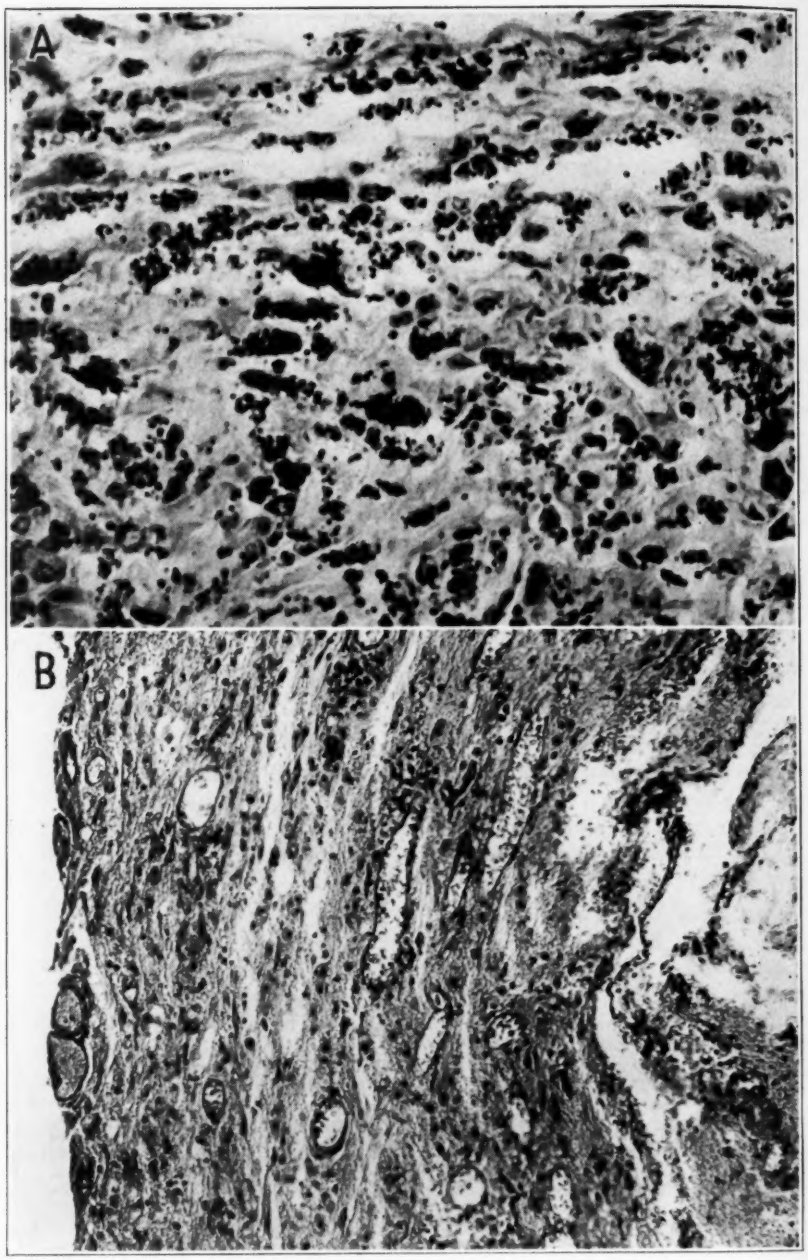

Fig. 2.—*A* (case 5), hematoma wall. Innumerable particles of blood pigment (black in the photograph) have been taken up by large phagocytic cells. Hematoxylin and eosin; reduced from a magnification of 375.

B (case 6), hematoma wall. The numerous young blood vessels, fibroplasia and round cell infiltration resemble granulation tissue. Hematoxylin and eosin; reduced from a magnification of 120.

weeks before admission. In both attacks the numbness of the left arm also recurred, and, after the last attack, the symptoms grew rapidly worse. Headaches were severe and vomiting was frequent. He was confined to bed by vertigo and had severe tinnitius on the left; the numbness involved the left side of the face and trunk and the lower left extremity, and he was very awkward in using his left hand. He had diplopia and tended to strangle on swallowing.

On examination, he was drowsy and yawned frequently. There was moderate early papilledema. The left pupil was smaller than the right; the left external rectus muscle was very weak, and he had coarse nystagmus, most marked on left lateral gaze. The fifth, seventh, eighth and ninth cranial nerves on the left showed marked impairment of function. There were moderate left hemiparesis and marked left hemihypesthesia. The left extremities were violently ataxic.

Operation (Aug. 30, 1939).—A bilateral suboccipital craniectomy was done. The left cerebellar hemisphere was enlarged, and its folia were widened. An exploring cannula entered a cyst, 3 cm. beneath the surface, containing old, viscid, chocolate brown blood. An incision was made down to the cyst. There was no definite capsule, but the wall was composed of old, rather tough clot, which was adherent to the adjacent cerebellar tissue. Subsequent microscopic study showed no evidence of neoplasm (fig. 2*B*). The hematoma had compressed the left side of the brain stem. It was completely evacuated and as much of the wall as possible was removed.

The patient made a satisfactory recovery, although some ataxia persisted for almost six months. In the twelve months after operation he had three transitory "faint and dizzy feelings," but none has occurred in the past six months. There have been no symptoms suggestive of recurrence of the hemorrhage.

CASE 7 (referred by Dr. Curtis B. Johnson, Earlington, Ky., and Dr. Robert L. Bone, Madisonville, Ky.).—Mrs. M. L., aged 62, had had many attacks of gallstone colic. While recovering from an attack two and a half years before admission, she suddenly lost consciousness and "shook all over." Subsequently she could not speak or move her right arm or leg. She recovered slowly and after six months had no residual symptoms except inability to multiply or divide. Five months later she began to have occasional typical jacksonian convulsions, beginning in the right hand, with no residual paralysis or aphasia. Two weeks before admission she began to have these seizures every few minutes and gradually sank into stupor, the attacks occurring almost continuously.

On admission she was semistuporous, but was having innumerable brief clonic seizures involving the right side. When roused she could speak only indistinctly and with marked perseveration, but she was oriented in all spheres. The optic disks were normal. There was right hemiplegia, but no spasticity, Hoffmann sign, reflex grasping, Babinski sign or clonus. Deep reflexes were not elicited on the right. Sensation was greatly impaired over the entire right side. Roentgenograms showed a small area of calcification in the posterior left frontal region. There was no hypertension or demonstrable arteriosclerosis.

Operation (Aug. 1, 1938).—A left frontal bone flap was reflected. In the premotor region an area of cortex, 4 cm. in diameter, was discolored and soft. A cortical incision disclosed a firm, yellowish capsule just beneath the surface. From its interior was obtained the thick brown fluid characteristic of an old hematoma. The capsule was removed en masse, except for several fibrous bands which extended into the surrounding cortex.

Convalescence was stormy. Bronchopneumonia developed, from which the patient recovered, only to have a flare-up of her long-standing cholecystitis, with

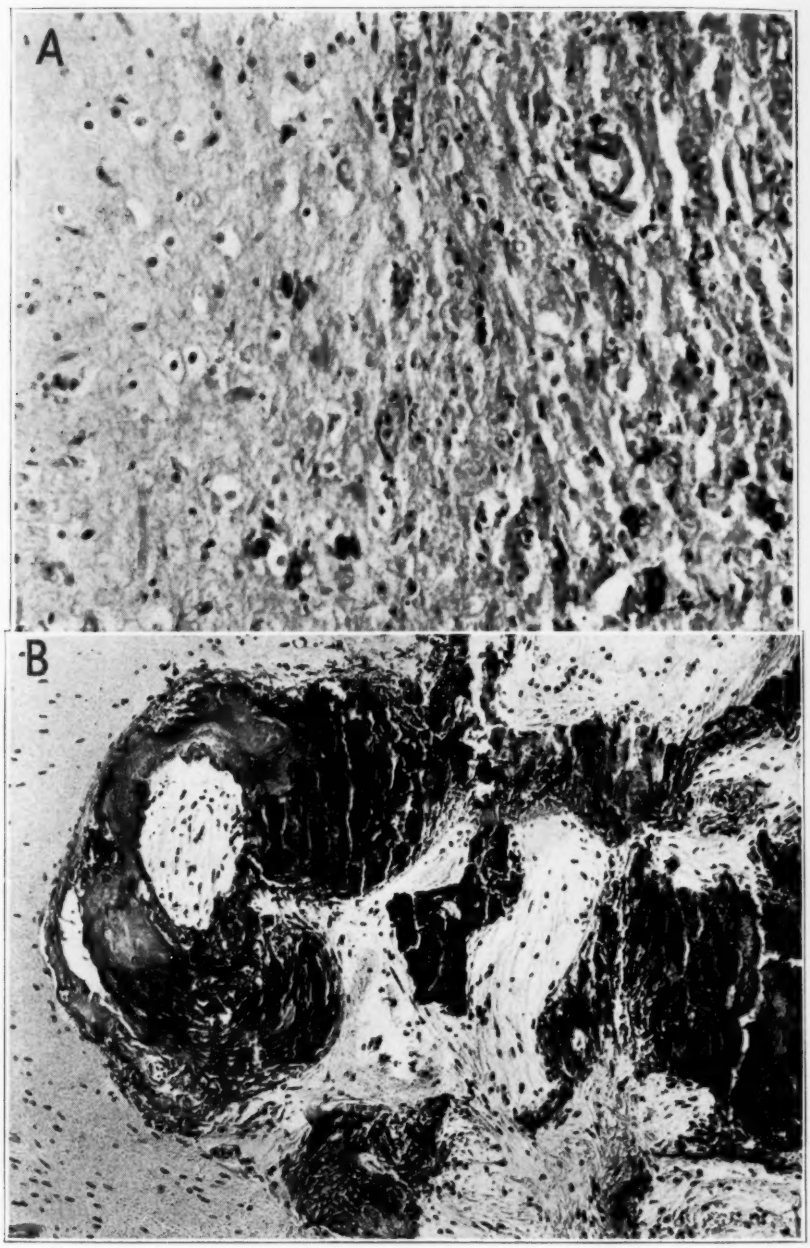

Fig. 3.—*A* (case 7), hematoma wall. The dense, avascular, elastic fibrous tissue at the right merges imperceptibly with the cerebral tissue at the left. Numerous small deposits of calcium are seen. Hematoxylin and eosin; reduced from a magnification of 225.

B (case 3), hematoma wall. Heavy calcification in a long-standing hematoma. Hematoxylin and eosin; reduced from a magnification of 120.

empyema of the gallbladder. The gallbladder was drained and a large number of gallstones removed by Dr. Alfred Blalock. She was finally discharged, five weeks after craniotomy. At this time voluntary motion was returning in the right extremities and she could speak a few words. Her progress at home was slow and retarded by renewed pulmonary complications. She died six months after operation, apparently of bronchopneumonia.

The final case must be presented separately because of two elements of doubt. First, there was a history of trauma, which seems unlikely to have been an etiologic factor in the cerebral hemorrhage. Second, the diagnosis was confirmed only by aspiration, and the possibility of hemorrhage into an infiltrating tumor therefore exists, although this, too, seems unlikely.

CASE 8.—B. J., a 56 year old Negro, who looked (and probably was) fifteen years older than his stated age, ten years prior to admission had sustained a blow on the head, followed by unconsciousness for an hour, but no subsequent symptoms. For three years he had suffered from progressive symptoms of arteriosclerotic heart disease, with frequent attacks of severe dyspnea, palpitation and precordial discomfort. One year before admission he had a sudden violent headache with "flashes of light in the right eye" (i. e., in the right visual field). These attacks recurred with increasing frequency until they occurred several times daily. He was often dizzy and unsteady on his feet, but had no localized weakness or change in sensation.

On admission, the blood pressure was 125 systolic and 75 diastolic, but he had advanced general and retinal arteriosclerosis, cardiac enlargement and signs of impending decompensation. The optic nerve heads were normal. There was right homonymous hemianopia, but no other neurologic signs. The cerebrospinal fluid pressure was 225 mm. of water. Roentgenograms showed a marked shift of the calcified pineal body to the right.

Operation (March 30, 1939).—With the patient in a sitting position, a burr hole was made over each occipital pole. Air (10 cc.) was first injected into the right ventricle. The cannula was then inserted on the left and, at a depth of 7 cm., entered a hemorrhagic cyst. About 10 cc. of thick, old blood was removed and replaced with air. Roentgenograms showed the cyst deep in the left parietal lobe with the ventricles displaced to the right (fig. 1 *B*).

Because of the patient's age and enfeebled condition and the likelihood that no neoplasm was present, no further procedure was undertaken.

The day after operation the hemianopia had disappeared. He had no further headaches and was discharged after treatment of his cardiac condition. Two months later the headaches and hemianopia returned. He was readmitted to the hospital, and the cyst was again aspirated. At this time the fluid was dark yellowish brown and very viscid. Symptoms were again relieved. He failed to return to the clinic according to instructions, and it was finally learned that he died at home nine months after the original aspiration. The cause of death was not known.

COMMENT

The most significant features of the 8 cases are shown in the accompanying table. Except for the etiologic factor, there were no essential differences between the cases of traumatic and those of spontaneous hemorrhage, and they will be discussed together.

Tabulation of Eight Cases of Subcortical Hematoma

Case No.	Age, Years	History of Trauma; Time Before Admission	Duration of Symptoms	Principal Clinical Phenomena	Location of Hemorrhage	Type of Hematoma	Operative Procedure	Result
1	5	20 hr.	20 hr.	Stupor, right hemiplegia, aphasia; bloody spinal fluid	Left temporal	Fresh, liquefied blood	Aspiration	Complete recovery (3 years)
2	16	9 days	9 days	Drowsiness, right hemiplegia, aphasia; focal convulsions	Left parietal	Solid, unencapsulated clot	Open evacuation	Complete recovery (7 years)
3	25	19 yr.	3 mo.	Generalized convulsions; normal spinal fluid	Right parietal	Old, calcified, cicatricial mass	Complete excision	Recovery; 2 minor seizures in 4 years
4	19	None	2 days	Sudden left hemiplegia, stupor; rising blood pressure; single convulsion; bloody spinal fluid	Right temporoparietal	Semisolid, unencapsulated clot	Open evacuation; subtemporal decompression	Gradual recovery; still improving (10 weeks)
5	38	None	9 mo.	Sudden right hemiplegia and aphasia; late focal convulsions; normal spinal fluid	Left parietal	Encapsulated liquefied hematoma	Complete excision of sac	Complete recovery (3 years)
6	27	None	11 mo.	Left hemihypesthesia, hemiparesis, ataxia and cranial nerve palsies; choked disks	Left cerebellar hemisphere	Encapsulated liquefied clot	Evacuation; partial removal of capsule	Recovery, with mild residual ataxia (1 year)
7	62	None	2½ yr.	Sudden hemiplegia with aphasia; focal convulsions; normal spinal fluid	Left premotor area	Old, encapsulated liquefied clot with calcification in capsule	Complete excision of sac	Slow improvement; death at home 6 months later, of unknown cause
8	56	10 yr.*	1 yr.	Arteriosclerotic heart disease; sudden right homonymous hemianopia; normal spinal fluid	Left occipitoparietal	Liquefied clot	Aspiration	Recurrence of symptoms after 2 months; death at home after 9 months

* The trauma was probably not of etiologic significance (see text).

Etiologic Factors.—In such instances as cases 1 and 2 the etiologic role of trauma cannot be questioned, although its exact mechanism cannot be explained. In the cases of spontaneous hemorrhage, however, the cause is by no means clear. Numerous explanations for spontaneous intracerebral hemorrhage (usually of capsular type) have been suggested: miliary aneurysm (Charcot and Bouchard,[11] Bagley [12]); fatty degeneration of vascular walls (Hamilton [13]), and toxic or infectious factors (Marburg,[14] Löwenstein,[15] Diamond,[16] Rand [17]). These and other etiologic possibilities have been reviewed by Craig and Adson.[18] It must be pointed out that conclusive evidence is lacking in the majority of reported cases. In my cases, no light is shed on this puzzling question. Preexisting arterial disease was known to be present in only 1 instance (case 8). Syphilis was not present in any case, and the cholecystitis in case 7 was the only preexisting or intercurrent infection.

Age.—It is striking that in 6 of the 8 cases in this series the patients were under middle age and that 3 of the patients were under 20. That this is not particularly unusual has been pointed out by Hawthorne,[19] who reviewed the literature on intracerebral hemorrhage in young people and reported 2 cases of his own. In 6 of the 9 cases of Craig and Adson [18] the patients were under 40.

Location.—In all 3 cases reported by Naffziger and Jones [20] in 1928 the hemorrhage was posterior temporal or parietal. The frequency of this location was reiterated by Naffziger [21] in 1936, and is well borne out by the cases of Craig and Adson,[18] Furlow, Carr and Wattenberg [22] and

11. Charcot, J. M., and Bouchard, C.: Nouvelle recherches sur la pathogéne de l'hémorrhagie cérébrale, Arch. de physiol. norm. et path. **1**:110, 643 and 725, 1868.

12. Bagley, C., Jr.: Spontaneous Cerebral Hemorrhage: Discussion of Four Types, with Surgical Considerations, Arch. Neurol. & Psychiat. **27**:1133 (May) 1932.

13. Hamilton, D. J.: A Text-Book of Pathology, Systematic and Practical, New York, Macmillan & Company, 1894, pt. 2.

14. Marburg, O.: Zur Frage der Hemorrhagia cerebri bei jüngeren Menschen und deren differentieller Diagnose, Deutsche Ztschr. f. Nervenh. **105**:22, 1928.

15. Löwenstein, E.: Tuberkelbazillämie bei Erkrankungen des Zentralnervensystems, München. med. Wchnschr. **78**:1080, 1931.

16. Diamond, I. B.: Brain Changes in Malignant Endocarditis, Arch. Neurol. & Psychiat. **27**:1175 (May) 1932.

17. Rand, C. W., in discussion on Naffziger and Jones.[20]

18. Craig, W. McK., and Adson, A. W.: Spontaneous Intracerebral Hemorrhage: Etiology and Surgical Treatment, Arch. Neurol. & Psychiat. **35**:1 (Jan.) 1936.

19. Hawthorne, C. O.: Cerebral and Cerebellar Haemorrhages in Apparently Healthy Adolescents and Children, Practitioner **109**:425, 1922.

20. Naffziger, H. C., and Jones, O. W.: Late Traumatic Apoplexy, California & West. Med. **29**:361, 1928.

21. Naffziger, H. C., in discussion on Craig and Adson,[18] p. 716.

22. Furlow, L. T.; Carr, A. D., and Wattenberg, C.: Spontaneous Cerebral Hemorrhage: The Surgical Treatment of Selected Cases, Surgery **9**:758, 1941.

the present series. Spontaneous hemorrhage into the cerebellum is rare. Seven cases were recorded by Charcot and Bouchard [11] in 1868. According to Torkildsen,[23] Bashan collected 55 cases and Durand-Fardel 13 cases. A case was reported by Hird [24] in 1910 and others by Kron and Mintz,[25] Thyne,[26] Hawthorne [19] and Bagley.[12] Recent papers on the subject have been published by Torkildsen,[23] Müller,[27] Echols [28] and Evans, Friedman and Courville.[29]

Symptoms.—The most characteristic feature of the clinical picture is its sudden onset, whether as a result of trauma or spontaneously. However, in only 1 of the cases of spontaneous hemorrhage (case 7) was immediate loss of consciousness the first symptom. In cases 4 and 5 unconsciousness followed the rapid development of hemiplegia, and in cases 6 and 8 it did not occur. In neither of the last 2 cases would it have been expected, because of the location of the lesions (cerebellar and parieto-occipital, respectively) and because the histories were suggestive of repeated small hemorrhages. Signs of marked increase in intracranial pressure are found only in the early stages, but their severity in cases 1, 2 and 4 suggests that many patients with subcortical hemorrhage may die without the accessibility of the lesion being appreciated.

The cerebrospinal fluid contained blood in the 2 cases of the earliest stages of hemorrhage in this series, suggesting leakage into the inferior horn of the ventricle (temporal in location in both instances).

Convulsions occurred in 5 of the 8 cases. In 3 of these the seizures were definitely focal. In the other 2 the pattern of the attacks could not be definitely ascertained.

The pineal body was shifted in 1 case, and calcification of the capsule could be visualized in the roentgenograms in 2 others.

The localizing neurologic picture is, of course, dependent on the area of the brain which is involved and is referable to that area.

Diagnosis.—It is worthy of note that in cases 3, 4, 5, 7 and 8 the diagnosis of subcortical hematoma was made prior to operation. In 1 of

23. Torkildsen, A.: Spontaneous Intracerebellar Hemorrhage Treated by Operation, Zentralbl. f. Neurochir. **2**:242, 1937.

24. Hird, A. E. W.: A Case of Cerebellar Hemorrhage, Lancet **2**:734, 1910.

25. Kron, I., and Mintz, W.: Kleinhirnblutung, geheilt durch Operation, Deutsche med. Wchnschr. **53**:1054, 1927.

26. Thyne, W.: Case of Cerebellar Hemorrhage Presenting Well-Marked Early Cervical Opisthotonus and Kernig's Sign, Lancet **1**:397, 1901.

27. Müller, W.: Tödliche Spontanblutung des Kleinhirns bei einem 19jährigen Mädchen, Zentralbl. f. allg. Path. u. path. Anat. **71**:433, 1939.

28. Echols, D.: Cerebellar Hematoma, Univ. Hosp. Bull., Ann Arbor **3**:10, 1937.

29. Evans, H. S.; Friedman, A. P., and Courville, C. B.: Calcification of Small Vessels of the Cerebellum: Report of Two Cases with Traumatic Hemorrhage, Bull. Los Angeles Neurol. Soc. **5**:18, 1940.

these (case 8) it would probably not have been made had the shift of the pineal body not been discovered. On the other hand, in retrospect, it might have been suspected in case 6. In case 2 the picture was clouded by the depressed fracture.

The diagnosis is much more difficult in very early than in the later stages. If trauma has occurred, extradural or subdural hemorrhage may be suspected. Fortunately, these conditions also call for operative therapy. If there has been no trauma, the diagnosis will be suggested by delay in or absence of loss of consciousness and by sharp localization of the initial, sudden symptoms to one limited region (i. e., to one extremity). This suggests a subcortical, rather than a deeper, lesion.

At later stages additional confirmation will be furnished by such manifestations as intermittent attacks, with gradual recovery between them; convulsive seizures, usually jacksonian in type; absence of progressive increase in intracranial pressure; calcification in the capsule of the hematoma; shift of the pineal body, and encephalographic or ventriculographic findings, in selected cases.

Pathologic Changes.—Penfield [30] has called attention to the characteristic discoloration of the cortex overlying a subcortical hematoma. This was present in 4 of the cases reported here. It may be added that this discolored area presents a definite soft consistency, even when a firm capsule lies beneath.

From a study of the lesions in this series, the following gross progression of the lesions may be postulated:

In the very early stages (first few days), the fresh, semisolid clot is surrounded by only the compressed cerebral tissues (case 4). The brain is tense, and there is marked venous distention. In the intermediate period (two weeks to one year), there is locally increased vascularity, encapsulation takes place (Robinson [7]) and the contained blood gradually loses much of its pigment, becoming yellowish brown. The capsule thickens, but in this period (case 5) can be easily stripped from the surrounding cerebral tissue. During the passage of years, the capsule grows steadily thicker and the cavity smaller, calcium is deposited in its walls and "fingers" of fibrous tissue extend into the surrounding brain. The brain reacts with gliosis and contracture (cases 3 and 7). If repeated hemorrhages occur, laminated clots may be found (Craig and Adson [18]). In case 6 a tendency toward this phenomenon was shown.

Confirmation of the stages of progression suggested in the preceding paragraph presents itself in a study of the histologic structure of the capsules. In case 5, in which the hematoma was of nine months' duration, the outstanding feature was extensive phagocytosis of blood pigment (fig. 2 *A*). In case 6, at a little later stage, there were numerous blood

30. Penfield, W., in discussion on Craig and Adson,[18] p. 716.

vessels and proliferating fibroblasts, with lymphocytic infiltration, suggesting the appearance of granulation tissue (fig. 2 *B*). On the other hand, at a later period, there are dense, elastic connective tissue, diminished vascularity, little inflammatory reaction, early calcification and involvement of the surrounding cerebral tissue in the scar (fig. 3 *A*). Finally, after many years, very heavy calcification may take place (fig. 3 *B*).

Operative Treatment.—The fact that in certain selected cases intracerebral hemorrhage is amenable to surgical therapy is only beginning to be recognized, although early operative procedures were reported by Cushing [31] and Russell and Sargent.[32] More recently, in selected cases operation has been performed by Kron and Mintz,[25] Naffziger and Jones,[20] Bagley,[12] Penfield,[33] Craig and Adson [18] (9 cases) and Furlow, Carr and Wattenberg [22] (5 cases). Nevertheless, one finds no mention of the operative treatment of these lesions in recent comprehensive publications by Munro [1] and by Gross and Ehrlich.[3] Friedman,[34] who recorded 2 cases in which treatment was by aspiration, stated: "The treatment is symptomatic. It includes . . . surgical interference . . . to exclude the presence of subdural clots. . . . The prognosis is usually grave."

The selection of cases for operation depends on the surgeon's ability to be reasonably confident that the hematoma lies sufficiently near the cortical surface to be accessible and that it is a solitary and localized lesion (see section on "Diagnosis").

The choice of the operative procedure must depend on the exigencies in the individual case, as illustrated by the variety of procedures adopted in the cases recorded here (fig. 4). In very early stages aspiration may be adequate. Accompanying decompression may be required by the vascular engorgement and swelling of the brain, as in case 4. Well encapsulated lesions should be radically extirpated.

Operative Results.—In the series of cases reported by Craig and Adson,[18] by Furlow, Carr and Wattenberg [35] and by me, there were no

31. Cushing, H.: Blood Pressure Reaction of Acute Cerebral Compression, Am. J. M. Sc. **125**:1017, 1903.

32. Russell, A. E., and Sargent, P.: Apoplectiform Cerebral Hemorrhage: Operation; Evacuation of Blood; Slow Improvement, Proc. Roy. Soc. Med. (Sect. Neurol.) **2**:44, 1909.

33. Penfield, W.: The Operative Treatment of Spontaneous Cerebral Hemorrhage, Canad. M. A. J. **28**:369, 1933.

34. Friedman, E. D.: Massive Intracerebral Hemorrhage of Traumatic Origin, in Brock, S.: Injuries of the Skull, Brain and Spinal Cord, Baltimore, Williams & Wilkins Company, 1940, chap. 6, p. 123.

35. Footnote 22: One patient reported by these authors died six weeks after operation, of pneumonia.

operative deaths. Of my 8 patients, 5 are restored to their normal occupations, with no disabling symptoms, and a sixth, whose case was the most recent, is recovering satisfactorily. The remaining 2 patients died months after operation, 1 of a condition other than the hematoma and 1 of unknown cause.

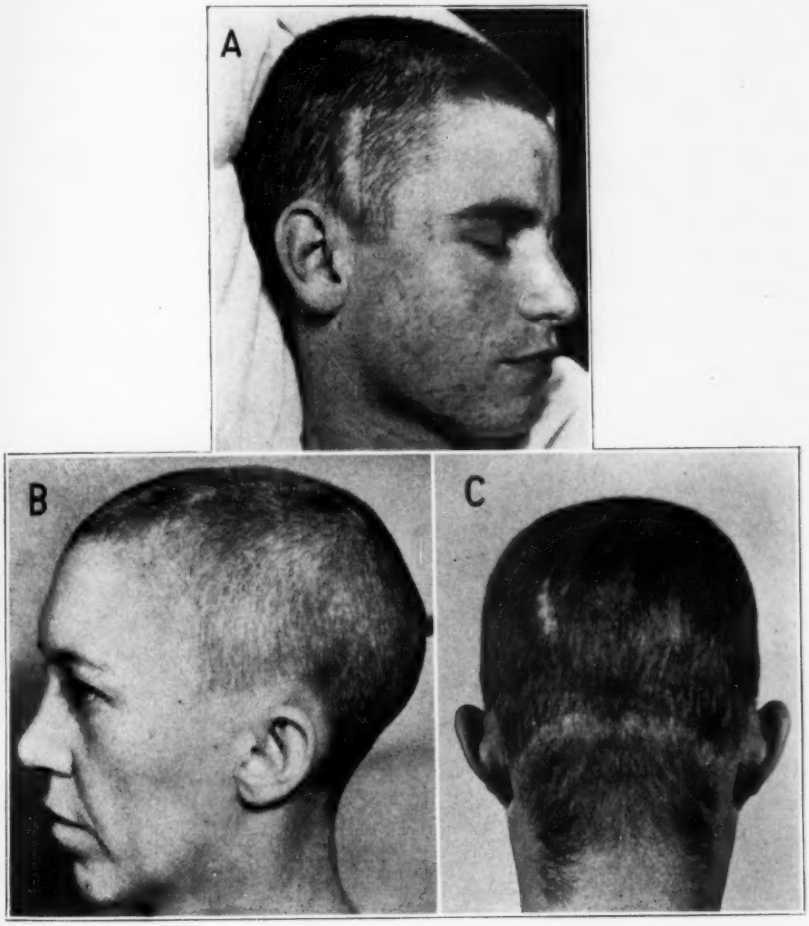

Fig. 4.—Photographs showing the incisions employed in several cases. *A*, (case 4), exploration through a subtemporal decompression opening; *B* (case 5), osteoplastic flap; *C* (case 6), suboccipital craniectomy. The small vertical incision at the left and above is identical with that employed for aspiration in case 8.

SUMMARY

Eight cases of solitary subcortical hematoma, in all of which the patients were subjected to surgical therapy, are reported.

In 3 cases hemorrhage was of traumatic origin, in 4 it was spontaneous and in the eighth the cause was doubtful.

The ages of the patients varied from 5 to 62 years, but 6 patients were under 40.

In 6 cases the location was temporal or parietal, in 1 frontal and in 1 cerebellar.

There were no operative deaths, but 2 of the patients died six and nine months later, respectively, 1 of pneumonia and 1 of unknown cause.

The symptomatology, diagnosis, pathology, operative treatment and surgical results are discussed.

NOTE.—Since this paper was submitted for publication, 2 additional cases of subcortical hematoma have been seen in this clinic. In both the hematoma followed trauma, occurred in middle-aged men and was in the frontoparietal region. One was seen forty-eight hours and the other ten months after injury.

HEPATOLENTICULAR DEGENERATION

REPORT OF A CASE

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The question whether the entity described by Kinnier Wilson should be expanded to include additional symptoms and signs reported by others in similar cases has been debated in the scientific literature for the past two decades. The case presented here is of interest because of the nature of the onset, the absence of tremor, the clinical methods used in an attempt to establish the presence of hepatic damage and the mental status and personality changes of the patient.

REVIEW OF LITERATURE

A brief review of the development of the concept of hepatolenticular disease reveals that the condition aroused interest before the time of Wilson and is probably not so rare as is generally believed.

Strümpell [1] in 1878 described a case in which the disease seemed to resemble multiple sclerosis but which was a typical instance of this condition; in 1883 Westphal [2] reported 2 similar cases of a disorder to which he gave the name pseudosclerosis. Gowers [3] reported another case under the name of "tetanoid chorea" in 1888, after which appeared case reports by Ormerod [4] and Homén [5] (1890, 1892). In all of these

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1. Strümpell, A.: Ueber diffuse Hirnsclerose, Arch. f. Psychiat. **9**:268-285, 1878.

2. Westphal, C.: Ueber eine dem Bilde der cerebrospinalen grauen degenerationähnliche Erkrankung des centralen Nervensystems ohne anatomischen Befund, nebst einigen Bemerkungen über paradoxe Contraction, Arch. f. Psychiat. **14**:87-134, 1883.

3. Gowers, W. R.: Tetanoid Chorea Associated with Cirrhosis of the Liver, in A Manual of Diseases of the Nervous System, London, J. & A. Churchill, 1888, vol. 2, p. 656.

4. Ormerod, J. A.: Cirrhosis of the Liver in a Boy, with Obscure and Fatal Nervous Symptoms, St. Barth. Hosp. Rep. **26**:57-68, 1890.

5. Homén, E. A.: Eine eigenthümliche bei drei Geschwistern auftretende typische Krankheit unter der Form einer progressiven Dementia mit ausgedehnten Gefässveränderungen, Arch. f. Psychiat. **24**:191-228, 1892.

cases there was a well defined syndrome with pathologic changes in both the central nervous system and the liver. In 1912 Wilson [6] published his classic paper. He described the disease, which he called progressive lenticular degeneration, as one occurring in young persons, often familial, fatal within a period varying from one month to seven years and characterized by "a symptom-complex whose chief features are: generalized tremor, dysarthria and dysphagia, muscular rigidity and hypertonicity, emaciation, spasmodic contractions, contractures, emotionalism." He stated that although cirrhosis of the liver is constantly present there are no signs of hepatic disease during life. The chief changes observed at autopsy were described as bilateral symmetric degeneration of the putamen and the globus pallidus. In the liver was a pronounced multilobular or a mixed type of cirrhosis with necrosis, fatty degeneration and regeneration.

Prior to Wilson's paper, however, Kayser [7] in 1902, Salus [8] in 1908 and Fleischer [9] in 1909 and 1912 had described the corneal pigmentation which is now accepted as a diagnostic sign. The first two authors stated that this sign was associated with multiple sclerosis. Rumpel [10] (1913) expressed the belief that the primary disease was pseudosclerosis and intimated that the corneal pigmentation was associated with hepatic disturbance.

Von Hösslein and Alzheimer [11] (1912) verified the microscopic lesions in the brain already observed by Wilson and Fleischer and described the pathognomonic giant glia cells in the corpus striatum; subsequent work by Fleischer brought about the recognition that pseudosclerosis and the corneal pigmentation occurred in the same cases.

Although other observers suggested the possibility of an association, it was not until 1921 that Hall,[12] in his presentation of 68 cases,

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6. Wilson, S. A. K.: Progressive Lenticular Degeneration: A Familial Nervous Disease Associated with Cirrhosis of the Liver, Brain **34**:295-509, 1912.

7. Kayser, V.: Ueber einen Fall von angeborener grünlicher Verfärburg der Kornea, Klin. Monatsbl. f. Augenh. **40**:22-25, 1902.

8. Salus, R.: Grünliche Hornhautverfärbung bei multiple Sklerose, Med. Klin. **1**:495-497, 1908.

9. Fleischer, B.: Die periphere braungrünliche Hornhautverfärbung als Symptom einer eigenartigen Allgemeinerkrankung, München. med. Wchnschr. **56**:1120-1123, 1909; Ueber eine der "Pseudosklerose" nahestehende bisher unbekannte Krankheit, Deutsche Ztschr. f. Nervenh. **44**:179-201, 1912.

10. Rumpel, A.: Ueber das Wesen und die Bedeutung der Leberveränderung und der Pigmentierung bei den damit verbundenen Fällen von Pseudosklerose, Deutsche Ztschr. f. Nervenh. **49**:54-73, 1913.

11. von Hösslein, C., and Alzheimer, A.: Ein Beitrag zur Klinik und pathologischen Anatomie der Westphal-Strümpellscher Pseudosklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **8**:183-209, 1912.

12. Hall, H. C.: La dégénérescence hépatolenticulaire, Paris, Masson & Cie, 1921, p. 361.

correlated progressive lenticular degeneration, pseudosclerosis and the corneal ring; he realized, however, that the ring was not always present and that the clinical symptoms were variable. Subsequently, many case reports [13] have been published. These indicate that while the disease is mainly a true extrapyramidal syndrome, variants exist and the symptoms may be evidence of pyramidal as well as extrapyramidal involvement and that the symptoms referable to the liver may overshadow those of the central nervous system for a time or symptoms of damage to both may be present; corneal pigmentation may or may not be demonstrated, and ocular changes, including pseudocataract and night blindness, may be present. Bothman and Rolf [14] reported a case in which microcephaly was associated with the syndrome.

As the observations referable to the disease increased, many theories were advanced to explain it. Wilson stated that the disease was not abiotrophic and expressed the belief that the cause was a toxin. Further work has led to the conception that the disease is due to endogenous rather than to exogenous factors; changes in the calcium level, distortion of the normal level of the blood lipids (with indications that the disease may be related to the lipoidoses) and changes in the mineral content of the body have been described. In line with this idea, Tsiminakis [15] reported an increased galactose output, a diabetic blood sugar curve and an increased bilirubin content of the serum. Richter [16] expressed the belief that the disease was an abiotrophy, a concept held by many more recent workers; Walsh [17] preferred the term "dysbiotrophy."

The corneal pigmentation has been extensively studied. Goldbach [18] stated that the nature of the pigment was still undetermined despite much work directed toward solving the problem. Theories that it is composed of silver, iron, copper, urobilin or hemosiderin no longer seem tenable;

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13. Harrow, R., and Richards, G. G.: Case of Progressive Lenticular Degeneration Associated with Cirrhosis of the Liver (Wilson's Disease), Internat. Clin. **3**:105-115, 1935. Baltzer, D. M.: A Hepato-Cerebral Syndrome (Wilson's Disease), Canad. M. A. J. **34**:544-545, 1936. Brouwer, B.: The Spleen, the Liver and the Brain, Proc. Roy. Soc. Med. **29**:579-592, 1936. Lidbeck, W. L., and Larson, C. P.: Hepatolenticular Degeneration: Report of a Case with Autopsy Findings, Northwest Med. **38**:201-204, 1939.

14. Bothman, L., and Rolf, D. E.: The Kayser-Fleischer Ring in Wilson's Disease and Microcephaly, Am. J. Ophth. **19**:26-33, 1936.

15. Tsiminakis, T.: Demonstriert zwei Fälle von Wilsonscher Krankheit mit Kayser-Fleischerschem Ring, Ztschr. f. Augenh. **75**:103, 1931.

16. Richter, H.: Beiträge zur Klinik und pathologischen Anatomie der extrapyramidalen Bewegungsstörungen, Arch. f. Psychiat. **67**:226-294, 1922.

17. Walsh, M. N.: Hepatolenticular Degeneration, Proc. Staff Meet., Mayo Clin. **11**:757-763, 1936.

18. Goldbach, L. J.: Kayser-Fleischer Ring—Wilson's Disease, Am. J. Ophth. **21**:1118-1128, 1938.

more commonly accepted is the explanation of Kubik [19] and of Poe [20] that it is an autochthonous pigment, probably a product of the endothelium. If the disease is a manifestation of disturbed metabolism, the possible relation of the ring to the hepatic degeneration is more easily postulated.

REPORT OF CASE

A white man aged 20 was admitted to the University of Chicago Clinics on March 28, 1940. He was suffering from polydypsia, polyuria with urgency and incontinence, anorexia, sialorrhea, dull epigastric pain, loss of muscular strength, retardation of muscular activity with slight incoordination, insomnia, apathy and depression, with crying spells at night. The patient had previously been healthy and had completed easily the freshman year in the engineering school of a state university in June 1939. Employed as a laborer through the summer and fall months, he had no difficulties until December 1939, when he noted mild malaise. However, he participated in competitive basketball through December. An elective submucous resection of the nasal septum for chronic sinusitis of ten years' duration was performed the first week of January 1940. There was no acute infection of the upper respiratory tract, exacerbation of the sinusitis, generalized infection or febrile reaction at this time. The operation was done with local anesthesia, but was followed by slow bleeding for several hours of a greater intensity than is usually expected. The patient displayed extreme apprehension over this incident. About a week later the aforementioned symptoms developed. The depression and changes in personality so dominated the clinical picture that the referring physician expressed the opinion that the patient should be treated in the psychiatric clinic.

The only significant events in the history were chronic sinusitis of ten years' duration, which had been productive of foul-smelling pus for several months of each year, and the appearance of an "enlarged salivary gland" on the left side of the neck at the age of 13. The latter opened spontaneously and was treated successfully with light therapy and roentgen rays. Roentgenograms of the chest taken then and on two other occasions revealed nothing important, and the reaction to a modified Mantoux test performed by the school physician was also negative. The patient was the oldest of 3 children of healthy, American-born, middle class parents, of English and Scotch lineage. There was no familial incidence of a similar disease.

Physical examination on entrance showed a tall, stooped person, carelessly dressed, with urine-soiled clothing. His arms hung in akinetic fashion; he moved slowly with awkwardness and increased effort. He was completely incontinent of urine and was irritated by constant urgency, despite the lack of control.

The skin was oily, with numerous comedos and sebaceous cysts; there was a livid flush over the malar and nasal regions; a few ecchymotic areas were present around the corners of the mouth, and superficial fissures at the angles were bleeding. The face was masklike, with dull eyes fixed in a stare; the mouth was open, and saliva drooled from it constantly; the tongue protruded in the midline, with a

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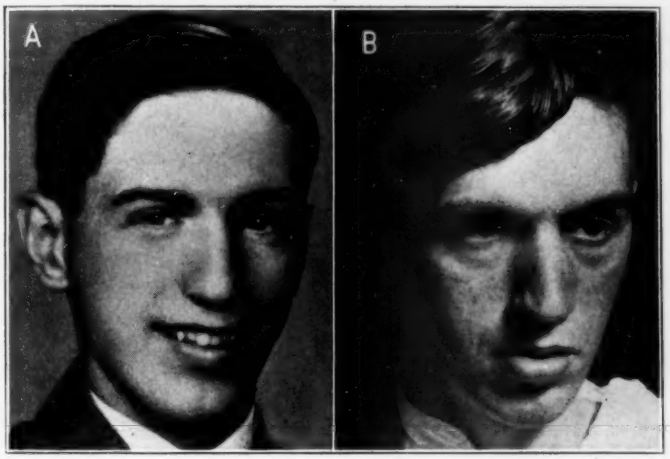
19. Kubik, J.: Zur Kenntnis des Kayser-Fleischerschen Ringes und zur Pathologie der Pseudosklerose und Wilsonschen Krankheit, Klin. Monatsbl. f. Augenh. **69**:214-218, 1922.

20. Poe, D. L.: Kayser-Fleischer Ring in the Cornea in a Case of Wilson's Disease, Am. J. Ophth. **13**:1045-1049, 1930.

coarse tremor. Its surface showed hypertrophied papillae, tiny superficial bleeding ulcers at the margins, redness and fissures suggestive of a "geographic tongue." A thick postnasal drip was observed in the throat; pharyngeal reflexes were present. The heart and lungs were normal; the blood pressure was 130 systolic and 60 diastolic on entrance, but it ranged from 180 to 110 systolic and 120 to 60 diastolic; the pulse rate was 94, and the beat was regular. On examination of the motor system it was found that there was weakness of all the muscles of the face and pharynx; dysphagia and dysphonia were present, and difficulty in breathing was experienced subjectively. Respirations were shallow but regular and adequate; deep respiration could be forced. A mild degree of generalized rigidity and spasticity was present. Coarse coordinating movements were well performed, but a fine tremor was apparent in some of the more detailed movements. Superficial and deep reflexes were unchanged; plantar stimulation gave a flexor response. There were no sensory changes on repeated examinations. The weight was 68.9 Kg.,



Photographs of J. S., taken (*A*) June 1939 and (*B*) April 1940.

which was 6 Kg. less than the average weight for a person of the age (20 years) and height (187 cm.) of the patient.

The patient appeared dull, listless and apathetic and apparently unconcerned by his distressing condition, but actually he was apprehensive, tense and depressed about it. He displayed poverty of expression in all spheres; his speech response and ideation were retarded, and he showed a tendency to use monosyllabic words. There were an increased reaction time, easy distractibility, inability to concentrate and lack of spontaneity. He was rather seclusive. Marked disturbance of sleep rhythm was observed; he would sleep only an hour or two, then waken and cry in a whining fashion, displaying great fear of being alone at these times. He was able to sleep soundly for periods of one to two hours once or twice during the day.

Laboratory studies gave the following results: The urine was normal except for the presence of sugar. In routine specimens (four daily) the reduction varied from 0 to 1 plus; only the admission specimen, with a 2 plus reaction, showed a heavier sugar content. White blood cells ranged from 7,650 to 8,700 per cubic millimeter, with a normal differential count; the hemoglobin was maintained at 14 Gm.

per hundred cubic centimeters (Newcomer) and the red blood cells at 5,000,000 cells per cubic millimeter. There was slight hypochromasia of the red cells. Young forms in either series were absent from the peripheral blood. The bleeding time was three minutes and the clotting time two minutes and forty seconds; the prothrombin in the blood serum was 65 per cent of normal. Dynamic responses on spinal puncture were within the normal range; the fluid was clear and contained 1 lymphocyte per cubic millimeter; the protein and dextrose values were normal. The Wassermann and the Kahn reactions of the blood and spinal fluid were negative. Values for the chemical constituents of the blood were as follows: nonprotein nitrogen 25 mg. per hundred cubic centimeters; urea clearance, determined by the square root method ($U/B \sqrt{V}$, in which U is urinary urea; B, blood urea, and V, urinary volume, cubic centimeters per minute), 34 and 55; cholesterol 201 mg. and cholesterol esters, 75 mg. per hundred cubic centimeters; total nitrogen 10.36 mg. per hundred cubic centimeters; total plasma proteins 6.4 Gm. per hundred cubic centimeters, and albumin 4.02 Gm. and globulin 2.32 Gm. per hundred cubic centimeters. The albumin-globulin ratio was 1.76. The results of serum studies were reported as follows: chlorides 103 millimols per liter; hydrogen ion concentration 7.43; carbon dioxide 29.5 millimols per liter; phosphorus 2.6 mg. per hundred cubic centimeters, and calcium 7 mg. per hundred cubic centimeters. The results of the van den Bergh test were within normal limits, as were those of the bilirubin and bromsulphalein excretion tests.

The Gray [21] colloidal gold test for hepatic function gave positive results. The hippuric acid test showed a reduction in the rate of excretion. The dextrose tolerance test on several occasions showed a diabetic type of curve.

The roentgenograms of the chest and skull were normal. Roentgenographic and direct examination showed severe chronic pansinusitis on the left side; laryngoscopy revealed weakness of the laryngeal muscles. A roentgenogram of the cervical portion of the spine showed it to be normal, but the picture was suggestive of compression of the left side of the trachea at the level of the sixth cervical vertebra.

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21. (*a*) The gold colloidal test on the blood serum gave a first zone curve on each of three occasions.

(*b*) Hippuric acid tests (Quick technic): All values are expressed in grams of benzoic acid detoxified.

1. First hour, 0.27 Gm.; second hour, 0.37 Gm.; third hour, 0.76 Gm.; fourth hour, 0.59 Gm.; total, 1.94 Gm.
2. First hour, 0.2 Gm.; second hour, 0.78 Gm.; third hour, 0.65 Gm.; fourth hour, 0.68 Gm.; total, 2.31 Gm.

(*c*) Dextrose tolerance tests. All values are expressed in milligrams per hundred cubic centimeters.

Oral: 1 Gm. dextrose per kilogram of standard weight.

1. Fasting, 78 mg.; one half hour, 142 mg.; one hour, 236 mg.; two hours, 162 mg.; three hours, 160 mg.
2. Fasting, 72 mg.; one half hour, 193 mg.; one hour, 246 mg.; two hours, 207 mg.; three hours, 134 mg.

Intravenous: 20 Gm. dextrose in four minutes.

1. Fasting, 99 mg.; 5 minutes, 214 mg.; 10 minutes, 169 mg.; 15 minutes, 198 mg.; 30 minutes, 175 mg.; 45 minutes, 167 mg.; 1 hour, 155 mg.

The thyroid gland was not palpable clinically, and the basal metabolic rate was +4 per cent. Fluoroscopic and roentgenographic studies of the gastrointestinal tract subsequent to these observations showed that the esophagus, stomach and duodenal bulb were normal. No evidence of esophageal varices was present. Urologic consultation indicated that the symptoms relative to the genitourinary tract were systemic rather than local. An electroencephalogram showed slow swings in both frontal leads, more pronounced on the left and indicative of organic pathologic changes. The intelligence quotient as determined by the revised Stanford-Binet test was 116.

A Kayser-Fleischer ring was present in the cornea of each eye. Since Wilson stated that hepatolenticular degeneration is a familial disease, the sisters of the patient were examined for the characteristic hepatic damage by the Gray colloidal gold test and for the Kayser-Fleischer ring by the slit lamp method, but the results of both tests were negative.

The patient was put on a high caloric, high vitamin diet with supplementary thiamine hydrochloride, nicotinic acid and ascorbic acid and was given tincture of hyoscyamus, the initial dose being 20 drops three times a day, which gradually was increased to tolerance. He was in the hospital for a month, during which period he showed little change in any of the subjective or objective symptoms. The bleeding areas of the face and mouth healed, but the prolonged bleeding after lavage of the sinuses was unchanged. He continued to bruise easily. The malar flush and the seborrheic dermatitis improved. The motor activity was slightly increased, and he was occasionally able to exhibit a little facial expression. Insomnia was controlled to some extent by sedation. Two weeks after discharge he exhibited marked edema of the ankles, which extended up to the lower third of the tibias; with reduction of fluid intake and restriction of salt this disappeared. After another fortnight cystitis developed and all medication except the vitamins was waived to permit intensive therapy for this infection. During this period a coarse intention tremor of the left hand developed, which extended to the entire arm; the right hand continued to show a fine tremor. Greater rigidity and spasticity were apparent. There was a transient Babinski sign on the left. After the cystitis had subsided, hepatic function tests were repeated, with confirmatory results. Treatment with hyoscyamus was again instituted, which resulted in improvement of the tremor. Repeated physical examinations throughout the period since hospitalization have revealed no essential changes; although the patient can be said to be more comfortable and less apprehensive, little real improvement has been effected.

COMMENT

This case presented a diagnostic problem on entrance because of the factors suggestive of chronic encephalitis; however, the absence of any history of infection of the central nervous system, the abrupt afebrile onset in a person 19 years of age, the absence of a familial history of similar illness and the presence of a high, diabetic type of curve in the dextrose tolerance test, with little gross evidence of sugar in the urine, led to more detailed diagnostic studies. Poe stated that the presence of the Kayser-Fleischer ring is regarded by many authorities as pathognomonic of hepatolenticular degeneration. When the ring was observed in this instance, the case was studied in relation to others in

these clinics in which such a diagnosis had been made to determine whether or not hepatic damage could be demonstrated.

There were many indications in this case that damage to the liver might be present. On physical examination the area of hepatic dulness seemed decreased. The dextrose tolerance curves obtained on repeated examinations by both the oral and the intravenous method were diabetic in type, with little reducing substance in the urine. Since the intravenous route of administration of dextrose minimizes the possibility of faulty absorption in the gastrointestinal tract, it is fairly accurate to assume that the cause of the disordered sugar metabolism [22] must lie elsewhere. Hepatic damage, a cerebral lesion or true pancreatic diabetes seemed the most likely. With the usual methods of testing hepatic function (van den Bergh, bilirubin excretion and bromsulphalein tests) no abnormality was found. However, repeated hippuric acid tests showed a slight reduction in the rate of excretion.

On three occasions the colloidal gold reaction of the blood serum was determined according to Gray's method,[23] and in each instance was strongly positive. Since this reaction is a much more sensitive indicator than those already mentioned and since it has been found to be positive in other proved cases of hepatolenticular disease,[24] it was felt that it offered significant evidence of hepatic damage in this case. The cholesterol-cholesterol ester ratio was within the lower limits of normal, a finding that in similar cases warrants further investigation.

The patient was found to have prothrombin deficiency, the percentage of prothrombin being only 65 of the normal amount. He was given 2-methyl-1,4-naphthoquinone (menadione), 2 mg. four times a day, empirically to insure an adequate intake of vitamin K. Since the prothrombin deficiency was not improved under this treatment in the case of a patient who had adequate bile in the intestinal tract, it seemed that there must be an inadequate production of prothrombin, even though the absorption of vitamin K was adequate, a condition which may be interpreted as indicative of hepatic damage.[25]

While it is true that none of these tests can justify a definite diagnosis, the results of several point to organic disease of the liver and

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furnish presumptive evidence that such damage exists. These observations suggest methods by which hepatic function may be more adequately studied. In this case, it is felt that the presence of damage to the liver has been demonstrated before autopsy.

Whether or not a diagnosis of Wilson's disease can be made in the absence of tremor has long been controversial.[26] Except for the present case, the tremor was present when the patient was first seen in all the 9 cases in this institution in which such a diagnosis was made. The tremor of hepatolenticular degeneration is described in the literature as one of the most constant signs, although not always the most pronounced. It is a true tremor and is increased by excitement and by voluntary effort. In this case only a fine tension tremor of the outstretched hands could be detected on the patient's entrance and throughout his hospitalization, but on a visit to the clinic two months later a rhythmic tremor of the left hand on intention could be elicited. The diagnosis, however, was made on positive findings other than the tremor.

SUMMARY

A case of hepatolenticular degeneration is described, with emphasis on the mental status of the patient and the absence of tremor at the time the diagnosis was made. Attempts to demonstrate damage to the liver in the clinical state are discussed.

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MULTIPLE MENINGIOMA

REMOVAL OF TEN INTRACRANIAL TUMORS FROM A PATIENT

DEAN H. ECHOLS, M.D.

NEW ORLEANS

The rarity of multiple meningioma justifies the report of a case. Hosoi's [1] search in the literature in 1930 disclosed 22 cases, including 1 of his own. Raaf and Craig,[2] in 1935, found a case reported by von Anfimow [3] in 1889 which was not included in Hosoi's collected series. Since 1930 cases have been reported by Penfield and Young,[4] von der Hütten,[5] Uprus,[6] List,[7] Frazier and Alpers,[8] Alajouanine and co-workers,[9] Raaf and Craig,[2] Woltman and Love,[10] Harbitz,[11] Cerviño and

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From the Division of Neurologic Surgery, Tulane University of Louisiana School of Medicine.

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3. von Anfimow, J.: Ein Fall multipler Geschwülste in der Schädelhöhle, Neurol. Centralbl. **8**:484 (Oct.) 1889.

4. Penfield, W., and Young, A. W.: The Nature of von Recklinghausen's Disease and the Tumors Associated with It, Arch. Neurol. & Psychiat. **23**:320 (Feb.) 1930.

5. von der Hütten: Beitrag zur Diagnose von Hypophysentumoren, Ztschr. f. Laryng., Rhin., Otol. **24**:95, 1933.

6. Uprus, V.: Meningioma multiplex cerebri, Folia neuropath. estoniana **12**: 86, 1932; abstracted, Zentralbl. f. d. ges. Neurol. u. Psychiat. **67**:44, 1933.

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8. Frazier, C. H., and Alpers, B. J.: Meningeal Fibroblastomas of the Cerebrum, Arch. Neurol. & Psychiat. **29**:935 (May) 1933.

9. Alajouanine, F.; Petit-Dutaillis, D.; Bertrand, I., and Schmite, P.: Association chez une même malade de méningiomes multiples du cerveau, de fibrogliomes de l'acoustique et de fibrogliomes radiculaires, Rev. neurol. **41**:639 (Nov.) 1934.

10. Woltman, H. W., and Love, J. G.: Multiple Intracranial Meningiomas with Extension to the External Auditory Canal: Successful Removal; Presentation of Case, Proc. Staff Meet., Mayo Clin. **10**:497 (Aug. 7) 1935.

11. Harbitz, H. F.: Case of Multiple Meningiomas Combined with Diffuse Meningiomatosis with Remarks on Some Combinations of Multiple Tumors, Acta path. et microbiol. Scandinav. **12**:24, 1935.

associates,[12] Petit-Dutaillis and Ectors,[13] Arlt,[14], Puusepp,[15] Worster-Drought and associates,[16] Pacifico,[17] Cushing and Eisenhardt,[18] Dandy,[19] Horrax,[20] Larson and Stroud [21] and Armitage.[22] This brings the total number of reported cases to 52. The incidence of this condition is difficult to determine. Heuer and Dandy [23] had 1 case in 70 cases of tumors of the brain. Of 60 cases of meningioma among 315 histologically verified tumors of the brain studied by Horrax,[20] the growths were multiple in 4. Frazier and Alpers [8] collected a series of 75 cases of meningeal fibroblastoma, in only 1 of which the lesions were multiple.

Even rarer than their occurrence is the successful removal of these meningiomas. Heuer and Dandy [23] in 1916 reported the first case of successful removal of multiple meningiomas (two). Other cases in which the patients with multiple meningioma survived the operation were reported by Dandy,[19] Raaf and Craig,[2] Woltman and Love,[10] Puusepp and Cushing and Eisenhardt.[18] There were only two or three tumors in each case, except in those of Cushing and Eisenhardt [18] and Dandy.[19] Cushing and Eisenhardt's patient had five operations during a period of fourteen years. One meningioma was removed at each of the second, third and fourth operations. At the fifth operation numerous small meningiomas were removed, as well as a large, malignant parasagittal

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14. Arlt, H. G.: Multiple Meningiome des Gehirns und diffuse Meningiomatosis des Rückenmarks, Ztschr. f. d. ges. Neurol. u. Psychiat. **156**:713, 1936.

15. Puusepp, cited by Petit-Dutaillis and Ectors.[13]

16. Worster-Drought, C.; Dickson, W. E. C., and McMenemey, W. H.: A Multiple Meningeal and Perineural Tumor with Analogous Changes in the Glia and Ependyma (Neurofibroblastomatosis), Brain **69**:85 (March) 1937.

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23. Heuer, G. J., and Dandy, W. E.: A Report of Twenty Cases of Brain Tumor, Bull. Johns Hopkins Hosp. **27**:224 (Aug.) 1916.

growth. At the time of the report, about a year after the last operation, the patient had no complaints. Dandy [19] cited a case in which the patient was still living fifteen years after removal of one large and fifteen small meningiomas. In the following case ten meningiomas were removed.

REPORT OF A CASE

H. A., a 57 year old white farmer, was admitted to Charity Hospital in New Orleans, on Feb. 9, 1940, because of a headache, hemiplegia and stupor.

For one year the patient had experienced severe frontal headache. For six months generalized weakness, external strabismus of the left eye and progressive loss of weight were present. Shortly before admission there appeared left hemiparesis, mental confusion, nausea and vomiting. There were no convulsions. A thorough history was not obtained because the patient spoke a French dialect.

The principal neurologic findings were spastic left hemiparesis, paralysis of the left lateral rectus muscle, weakness of the right lateral rectus muscle, choked disks and stupor. There was no deafness.

Roentgenograms of the skull showed several small areas of calcification near the surface of the right occipital lobe and one near the vertex. Ventriculograms demonstrated a marked shift of the ventricular system to the left, with dilatation of the left lateral ventricle. The frontal horn of the right ventricle was depressed.

Operation (Feb. 28, 1940).—With local anesthesia, the right frontal lobe and parts of the parietal and temporal lobes were exposed. Because of the obvious underlying pathologic condition, the dura was opened in a stellate manner. Attached to the under surface of the dura were three meningiomas, the largest 1 cm. in diameter. They had produced depressions in the surface of the brain but did not adhere to the pia. The largest was at the posterior extremity of the middle frontal convolution, and the others were near the sylvian fissure. All these were excised, with their dural attachment. Exploration with the lighted retractor disclosed three pea-sized tumors near the postcentral convolution and one on the lesser wing of the sphenoid bone. These were scraped from the dura. As none of these small tumors explained the depression of the frontal horn of the ventricle shown in the roentgenogram, the frontal lobe was retracted from the falx. An oval tumor, measuring 5 by 4 by 2.5 cm., was found buried in the medial side of the hemisphere. This was scraped from its attachment to the falx and delivered. The resulting cavity was loosely packed with a single clump of wet cotton. Hemostasis was obtained by means of silver clips and electrocoagulation as the cotton was gradually tilted out and removed. During this process a glimpse was obtained of another tumor of the falx, posterior to the large one. Its removal led to the discovery of still another, almost as far posterior as the central sulcus. Both were 1 cm. in diameter and were attached to the falx at the inferior margin of the superior sagittal sinus. Since most of the exposed dura had been excised, the bone flap, still attached to the temporal muscle, was laid on the brain.

Postoperative Course.—The patient was discharged on the fourteenth postoperative day. The left hemiplegia was profound and the strabismus unchanged, but the small subtemporal decompression pulsated and the stupor had disappeared.

When last examined, on August 15, the spastic weakness of the left side of the body was present, but the patient could use the hand and could walk without assistance. He was alert, had gained weight and had no complaints except for the hemiparesis. The strabismus was still present.

Pathologic Report.—The large tumor and several of the small ones were examined by Dr. Louise Eisenhardt at the Brain Tumor Registry in New Haven, Conn. The diagnosis was multiple meningiomas, varying from type II, variant I, to type III, variant I.

COMMENT

Cushing and Eisenhardt [19] observed that more than one meningioma may be found in occasional cases of Recklinghausen's disease. They stated that "unilateral acoustic tumors occasionally, bilateral acoustic tumors more commonly, and bilateral acoustic tumors with centralized neurofibromatosis (neurinomatosis?) almost invariably are accompanied by tumors of the meninges." Accordingly, they reserved the term "multiple meningioma" for those conditions in which there is no recognizable trace of Recklinghausen's disease. This explains the occurrence of only 3 cases of multiple meningioma among the 295 cases of intracranial meningeal growths in Cushing's series. According to this strict definition, a number of the cases referred to in the opening paragraph would not be classified as instances of "multiple meningioma" because stigmas of neurofibromatosis were present. Since the patient presented in this paper showed neither acoustic nor cutaneous manifestations of Recklinghausen's disease, the case can be classified temporarily as one of multiple meningioma, as Cushing and Eisenhardt have defined it.

VASCULAR MALFORMATIONS AND VASCULAR TUMORS INVOLVING THE SPINAL CORD

A PATHOLOGIC STUDY OF FORTY-SIX CASES

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Relatively little has appeared in the literature concerning the vascular malformations and vascular tumors which affect the spinal cord, and certainly no very large series of cases has been studied. These space-occupying lesions, although not frequently encountered, form a very definite part of any large series of intraspinal surgical lesions. Rasmussen, Kernohan and Adson,[1] in a review of 557 intraspinal lesions, found that 8.5 per cent belonged to the group of extramedullary vascular tumors and that of 64 intramedullary neoplasms 7.5 per cent were of vascular origin. Individual case studies have appeared from time to time and will be referred to as they relate to the subject. The present study of 46 cases in which the treatment was surgical concerns particularly the pathologic aspects of these tumors and tumor-like formations.

CLASSIFICATION

The classification in table 1 is suggested by the cases which we have studied. It must be remembered, as has been pointed out by others, that any classification is useful only so long as it remains fluid. This is particularly true of the vascular tumors, of which rarely can any be said to be architecturally pure and in many of which gradations from the very simple to the very complex structure can be found.

For our purpose the vascular malformations may be defined as angiomatous developmental anomalies capable, under some circumstances, of further alteration in size and character. For clinical use they may be divided into those which may be regarded as hamartomas, developmental defects which at times take on certain of the characteristics of

From the Section on Pathologic Anatomy and Surgical Pathology, the Mayo Clinic (Dr. Kernohan).

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blastomatous lesions, and telangiectases, those which for practical purposes are static and mainly pathologic curiosities.

The classification used here follows that of Cushing and Bailey,[2] but differs in that an attempt is made to subdivide the vascular neoplasms further on the basis of their cellularity and activity. In addition, several examples of both clinically and microscopically malignant tumors were encountered and have been classed separately. It must be mentioned here, again, that the differentiation between hemangioma and hemangioblastoma is one of degree, the latter appearing as a more cellular and microscopically more active tumor than the former. Tumors presenting obvious gradations and mixtures of the different types have been encountered and have been classified according to the predominant

TABLE 1.—*Vascular Malformations and Vascular Tumors Involving the Spinal Cord*

I. Vascular malformations (18 cases)
(a) Telangiectasis
(b) Angioma (hamartoma)
1. Angioma venosum
2. Angioma arteriovenosum (angioma arteriale)
II. Vascular neoplasms (28 cases)
(a) Capillary
1. Capillary hemangioma (2 cases; 7.1 per cent)
2. Hemangioendothelioma (10 cases; 35.7 per cent)
3. Capillary hemangioblastoma (2 cases; 7.1 per cent)
(b) Cavernous
1. Cavernous hemangioma (7 cases; 25.0 per cent)
2. Cavernous hemangioblastoma (2 cases; 7.1 per cent)
(c) Sarcomatous
1. Hemangiosarcoma (5 cases; 17.9 per cent)

architecture. No attempt has been made to include in this study any detailed consideration of the cases of Lindau's disease and related conditions, which have been studied by Craig, Wagener and Kernohan.[3]

VASCULAR MALFORMATIONS

Telangiectases.—These are small vascular lesions, capillary in structure but with channels frequently larger than normal capillaries, which, in the nervous system, may be found particularly about the floor of the fourth ventricle and in the pons. Elsewhere in the body, the skin

2. Cushing, H., and Bailey, P.: Tumors Arising from the Blood Vessels of the Brain: Angiomatous Malformations and Hemangioblastomas, Springfield, Ill., Charles C. Thomas, Publisher, 1928.

3. Craig, W. McK.; Wagener, H. P., and Kernohan, J. W.: Lindau-von Hippel Disease: A Report of Four Cases, Arch. Neurol. & Psychiat. **46**:36 (July) 1941.

and mucous membranes are common sites for the lesion. Microscopically, it consists of a group of vascular channels having the typical structure of capillaries but frequently of sufficient size to be termed cavernous. The intervascular tissue most often shows no pathologic change, and, as Cushing and Bailey [2] have pointed out, in the nervous system the presence of glia and nerve tissue between the channels is proof of the anomalous character of the lesion. The literature on hereditary (familial) multiple telangiectasia (Osler's disease) has been reviewed by Goldstein [4] with particular reference to epistaxis, and it is of interest that in several instances involvement of the nervous system was noted. Also, Kufs [5] has described a case of familial telangiectasia with involvement of the central nervous system, although in his discussion no attempt was made to separate the various types of vascular lesions.

Whether this anomaly is capable of progressive change is not known, nor can the relation of this lesion to cavernous hemangioma or to angioma be defined. Such a relation suggests itself, however, in the case of certain of the angiomas which involve the cord incompletely or which are intramedullary. However, except for the progressive change to the more complex vascular anomalies and the rare instances of familial telangiectasia, this group is of little clinical importance.

Angiomas.—This group of hamartomas, consisting of the venous and the arteriovenous angiomas, is considered separately, since it is of distinct clinical importance and the lesions act in many ways like the neoplasms. The angioma is composed of large, tortuous and often abnormally formed vessels, which vary in form from the single, distended, thin-walled channel to the complex mass of interwoven arteries and veins. It may be purely venous, in which instance the vessels are deep blue, or it may be aneurysmal, in which case the vessels are often purple or purplish red and frequently pulsate. In some instances actual arteriovenous communications cannot be identified, but in others two distinct circulations can be demonstrated by the change in color of the contained blood when one or more of the vessels are compressed at the time of operation.

In the present series there were 18 cases of angioma, and in all but 6 of these the tumor could be classified as venous or arteriovenous. The differentiation is frequently difficult and, since this lesion is rarely excised, depends on the gross characteristics of the individual vessels, the presence or absence of pulsations and the color of the contained blood. Of the 18 cases of angioma encountered, only 3 were of women

4. Goldstein, H. I.: Hereditary Epistaxis With and Without Hereditary (Familial) Multiple Hemorrhagic Telangiectasia (Osler's Disease), Internat. Clin. **3**:148-170 (Sept.) 1930.

5. Kufs, H.: Ueber heredofamiliäre Angiomatose des Gehirns und der Retina, ihre Beziehungen zueinander und zur Angiomatose der Haut, Ztschr. f. d. ges. Neurol. u. Psychiat. **113**:651-686, 1928.

and the remaining 15 were of men. The average age for the entire group of patients was 38.8 years, with extremes of 25 and 64 years (table 2). To our knowledge, no case of angioma of the cord has been described in an infant, despite the apparently anomalous character of the condition.

Angioma Venosum: In 4 cases venous angioma was encountered. In 3 of these the lesion was in the epidural space and undoubtedly arose from the epidural venous plexus. In the fourth case the angioma involved the cord itself and probably arose from the pia. It consisted of a mass of angiomatous veins which were about five times the size of those normally present on the cord itself. There was no evidence of pulsation, and the vessels appeared thickened and sclerotic.

Of the 4 venous angiomas, 3 were present in the lower thoracic or the lumbar region. One was present in the cervical epidural space and consisted of a single large vessel, 0.5 cm. in diameter, with smaller com-

TABLE 2.—*Age Distribution of Eighteen Patients Having Angioma*

Age, Years	Venous	Arterio-venous	Undetermined Type	Total Number of Patients
21-30	2	3	2	7
31-40	1	1	0	2
41-50	1	2	3	6
51-60	0	1	0	1
61-70	0	1	1	2
Total	4	8	6	18

municating channels. This might be termed a simple varix, in contrast to the more complex lesions, which consisted of a mass of redundant and interlacing vessels. Of the other 2 extradural angiomas, 1 was in the lower thoracic region and the other involved the last lumbar and the first sacral segment. Both of these lesions consisted of a nest of large, wormlike, tortuous vessels, with no evidence of pulsation. In none of the cases was there any cutaneous vascular or pigmented nevus. No tissue was available for microscopic study from any of the tumors, all having been treated by ligation, coagulation and decompression.

Because of the character of the anomaly, there has been little chance to observe the intimate pathologic characteristics of the lesions. Benda [6] divided them into (1) phlebectasias (diffuse widening of the lumens of the veins), (2) varicosities (diffuse, irregular dilatations with circumscribed ampullar or saclike formations) and (3) venous angiomas, in which a circumscribed conglomeration of dilated veins occurs. The

6. Benda, C., cited by Globus, J. H., and Doshay, L. J.: Venous Dilatations and Other Intraspinal Vessel Alterations, Including True Angiomata, with Signs and Symptoms of Cord Compression, Surg., Gynec. & Obst. **48**:345-366 (March) 1929.

differentiation as to whether the lesion is a surface affair or involves the cord itself is of no significance, and it is probable, when the angioma is subdural, that there is involvement of the cord in a manner comparable to that in the brain. In the latter instance there is most often a wedge-shaped mass of vessels, which frequently reaches the ventricle, and intraventricular hemorrhage from this source is a not uncommon cause of death in such cases.

That progressive alteration of the normal vessels of the spinal cord to a condition comparable to angioma may occur with concomitant changes in the cord secondary to a pathologic change elsewhere is shown by figure 1, taken from MacLean.[7] This illustrates the distention of the anterior spinal veins with compression and destruction of cord tissue as

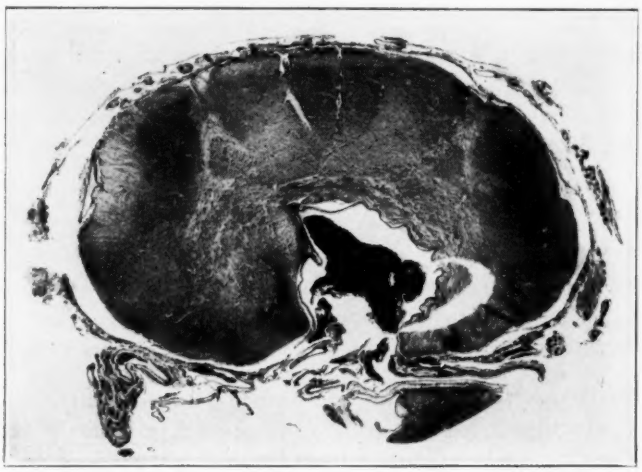

Fig. 1.—Cervical portion of the spinal cord, showing enlargement of the anterior spinal veins secondary to thrombosis of the superior longitudinal and lateral sinuses (from MacLean[7]). Note the compression and destruction of cord tissue. Hematoxylin and eosin; × 6.

a result of the collateral circulation established secondary to thrombosis of the superior longitudinal sinus, lateral sinuses and torcular Herophili in an 11 month old child. This condition is comparable in many respects to the simple venous varix, which it resembles anatomically.

Arteriovenous Angioma: Although comparable in many respects to venous angioma, this lesion differs in that there is both a physiologic and an anatomic arterial component. It is probable that in the fully developed anomaly the arterial elements are never present to the exclusion of the venous, and the term arteriovenous angioma is probably preferable to

7. MacLean, A. R.: Primary Thrombosis of the Superior Longitudinal Sinus with Chronic Obstruction, Thesis, University of Minnesota Graduate School, 1937.

angioma arteriale. Grossly, the lesion consists of a mass of tortuous and frequently pulsating vessels which contain blood varying from purple to purplish red and which have more the appearance of arteries than that of veins (fig. 2 *a*). However, both types of vessels may be present. At times definite arteriovenous fistulas are recognizable and the two circulations can be identified. In 1 instance it was possible, by compression of one of the vessels, to change the color of the angioma from purplish red to a deep blue, thereby proving beyond doubt the presence of two separate but intercommunicating circulations.

In 8 instances a typical arteriovenous angioma was encountered, and in 7 of these the lesion occupied the subdural space, having originated probably from the pia. In only 1 instance was the tumor intramedullary,

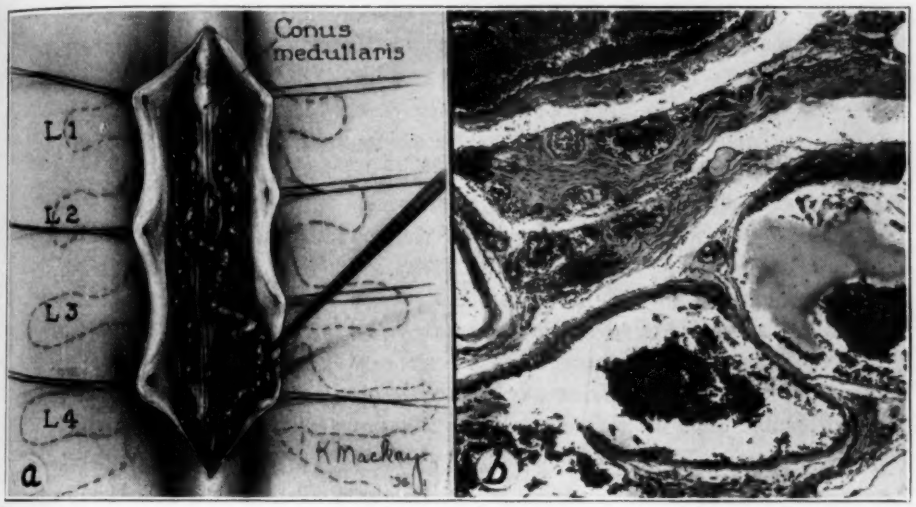

Fig. 2.—(*a*) Arteriovenous angioma exposed at the time of operation; note the enlarged and tortuous vessels and the manner in which these involve the cauda equina. (*b*) Portion of a resected angioma; note the poorly formed vessels and the intervening nerve root, which is the site of telangiectasis (hematoxylin and eosin; × 70).

and this was in the case of a 31 year old man in whom the lesion was in the cervicothoracic region and was visible only after the cord had been collapsed by evacuation of cystic contents. In this instance the dorsal midline artery of the cord was tortuous and elongated and measured 4 mm. in diameter. In none of the remaining 7 cases was the lesion situated at a level higher than that of the twelfth thoracic vertebra, and in no instance was an undoubted arteriovenous angioma encountered in the epidural space. In 7 cases the patients were men, and the average age of the patients was about 40.5 years, with extremes of 64 and 25 years.

Of particular interest in 1 case was the presence of an associated angioma, related to the intraspinal lesion, which involved the muscles and skin of the corrresponding metameres. This was the only case in the series in which the intraspinal lesion was associated with any evidence of a comparable lesion involving the skin or other soft tissues. According to Karshner, Rand and Reeves,[8] only 4 cases of hemangioma (angioma) of the cord associated with a nevus of the skin have been reported. In no other instance, so far as we are aware, has the associated cutaneous lesion involved the deeper soft tissues, with the presence of a bruit. In the case reported by Karshner and others an associated hemangioma of the vertebrae was present, and such a lesion was probably present in the case noted here, although there was no roentgenographic evidence of it. The angioma was epidural in the cases reported by Karshner and Johnston,[9] and was subdural, apparently arising from the pia, in the cases reported by Rand [10] and by Cobb.[11]

A little more is known of the pathologic characteristics of the arteriovenous angioma than of those of the venous variety. In the brain at least the vessels are often malformed, and Cushing and Bailey [2] have described characteristic nodular proliferation of the intima and of the media. In addition, there is often reduplication of the elastica interna, and vessels having the appearance of "arteriolized" veins are occasionally encountered. There is often direct involvement of the cord by portions of the varix, and in several instances the cord at operation had a nodular proliferation and contained cystic regions. Foci of infarction of the involved cord may be due to thrombosis of the vessels of the angioma with subsequent impairment of the circulation to the cord. Such regions of thrombosis are often visible at the time of operation, as was described by Cobb.[11] This may explain in part why return of function frequently does not follow operation and decompression of the involved region. Occasionally, evidence of old hemorrhage may be present in the form of yellow discoloration of the exposed nerve tissue.

In 1 case, the only one in the series, partial resection of the arteriovenous angioma was carried out and tissue obtained for microscopic examination. The tissue consisted of a group of thin-walled vessels, either in contiguity or with nerve root or areolar tissue intervening,

8. Karshner, R. G.; Rand, C. W., and Reeves, D. L.: Epidural Hemangioma Associated with Hemangioma of Vertebrae: Report of a Case, Arch. Surg. **39**: 942-951 (Dec.) 1939.

9. Johnston, L. M.: Epidural Hemangioma with Compression of Spinal Cord, J. A. M. A. **110**:119-122 (Jan. 8) 1938.

10. Rand, C. W.: Hemangioma of the Spinal Cord, Arch. Neurol. & Psychiat. **18**:755-765 (Nov.) 1927.

11. Cobb, S.: Hemangioma of the Spinal Cord, Ann. Surg. **62**:641-649 (Dec.) 1915.

rather than distinct channels. The majority of the vessels were of the venous type and were poorly formed, consisting in many instances of a layer of endothelium and a variable amount of connective tissue. In these, special stains revealed only a small amount of elastic tissue, although occasionally a typically venous channel was observed in which the elastic layer was developed out of proportion to the remainder of the structure. An occasional vessel was seen which had the structure of an artery, and although the Van Gieson stain disclosed the characteristic structure, the elastic laminas were poorly formed and were incomplete. In no instance was reduplication of the elastica interna or nodular proliferation of the intima or media observed (fig. 2 *b*).

In several regions, nerve root intervened between the individual vessels. In almost all instances this tissue was highly vascular and one band of such tissue was the site of telangiectasis, containing multiple channels of typical capillary structure packed with erythrocytes. Small vessels were scattered throughout the intervascular connective tissue, and an occasional one was the seat of thrombosis. Throughout the tissue there was evidence of a low grade inflammatory process in the form of small collections of inflammatory cells. These were present mainly in the intervascular tissue, although in some regions involvement of the individual vessels could be observed. There were no calcific deposits.

The interpretation of the foregoing observations must necessarily be incomplete, since but a small portion of the whole lesion was available for microscopic examination. It is significant, however, that despite the gross appearance of an arteriovenous angioma, with distended purple and pulsating vessels, the microscopic appearance was more that of the venous variety. It would appear that the resection included a greater portion of the venous than of the arterial elements. However, the poorly formed, thin vessels are not unusual in the aneurysmal type of angioma, and the occasional channels with overdeveloped elastica suggest "arteriolization" of a venous structure, a process compatible with a seven and a half year history.

VASCULAR NEOPLASMS

In the group of vascular neoplasms, there were 28 available for study; only those are discussed in which there was sufficient tissue available for detailed microscopic study and classification. Of this group, 15 were extradural, 10 were in the subdural space (extramedullary, apparently having originated from the pia) and 3 were intramedullary. Of the last, 1 was associated with syringomyelia of the cervicothoracic portion of the cord. As in any large group of neoplasms, the greatest number were in the thoracic region, 20 of the 28 tumors having been situated here. There were 4 cervical tumors and 1 cervicothoracic tumor. Of the remainder, 2 were confined to the lumbar region and 1 extended throughout the lower lumbar and the upper sacral region. The growths were evenly

distributed as to sex, 14 occurring in men and 14 in women. The age distribution was not unusual, with extremes of 23 and 67 years (table 3). Classification of the tumor type was made on the basis already discussed, and the characteristics of each group will be discussed individually.

Capillary Hemangioma.—Two examples of this type of growth were encountered, both tumors being in the extradural space and both being situated in the midthoracic region. Grossly, 1 of the tumors was yellowish red and appeared to have projections into the intervertebral canals, while the other was rather firm and on palpation gave the impression of central calcification. Both growths appeared well encapsulated, and both were rather vascular.

Microscopically, both tumors were composed of capillary elements with little other than the flattened endothelium forming the intervascular septums. In both tumors the vascular channels formed by the network of endothelial cells were somewhat larger than capillary size, but only in

TABLE 3.—*Age Distribution of Twenty-Eight Patients Having Intraspinal Vascular Neoplasm*

Age, Years	Number of Patients
21-30	5
31-40	7
41-50	6
51-60	7
61-70	3

occasional places were the sinuses large enough to be termed cavernous. There were scattered regions in which considerable cellular tissue intervened between the channels, but in both cases the capillary structure of the tissue was characteristic (fig. 3 *a* and *b*). In both growths a moderate amount of lipomatous tissue was present in the form of large fat cells.

Both tumors had thin, poorly formed capsules, and in both the stroma consisted of scattered strands of cellular connective tissue in which a few well formed blood vessels were present. The latter were present in moderate numbers in 1 of the growths and were relatively infrequently seen in the other. Mitotic figures were seen in only 1 of the tumors, and then rarely, and in 1 a few scattered foci of calcification could be identified. Degenerative and retrogressive changes were at a minimum, and the characteristic cystic spaces of extensive granular degeneration were absent. There were no regions of hyalinization, and the tumor tissue was well preserved.

Microscopically, both of these tumors had the appearance of relatively slow-growing neoplasms, with little evidence of any degree of cellular activity. The presence of moderate amounts of fat tissue in both tumors suggests an origin from the epidural fat. This is to be

differentiated from the fatty degeneration which takes place in the more cellular vascular tumors to form the characteristic "pseudoxanthomatous" cells.

Capillary Hemangioendothelioma.—This variety of vascular tumor, of which there were 10 examples, differed from the foregoing growth in that it exhibited a greater degree of cellularity, was more compact and contained newly formed vascular elements which were capillary both in size and in structure. Of the 10 tumors, 3 were situated in the extradural

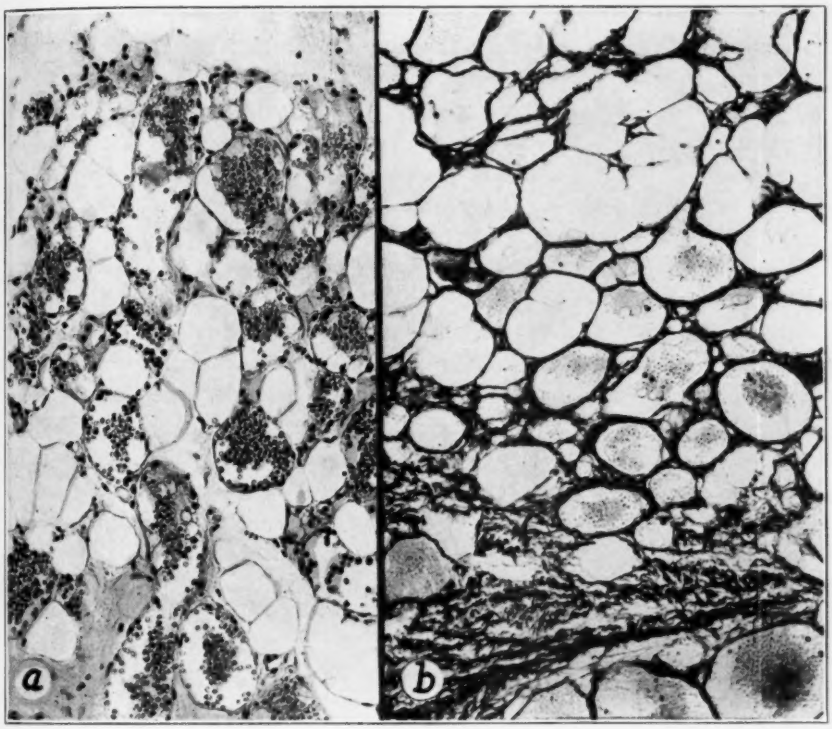

Fig. 3.—(*a*) Capillary hemangioma; note the vascular channels formed by the flattened endothelial cells with occasional small cell groups (hematoxylin and eosin; × 150). (*b*) Perdrau stain of another region of the same tumor, showing the characteristics of the stroma; note the occasional channels which are cavernous (× 150).

space, 5 were extramedullary but subdural and 2 were intramedullary. Of the last, 1 was associated with syringomyelia of the cervicothoracic portion of the cord. None of the tumors was in the lumbar region, although 1 was encountered in the sacral canal. Two were cervical, 6 were in the thoracic region and 1, as already noted, was in the cervicothoracic region.

In general, the gross appearance of the tumors varied with the location and certain individual characteristics of the lesion. The extradural tumors appeared most often as flattened, elongated masses, whereas the intradural growths were usually oval. The intramedullary tumors were both well circumscribed and tended to be elongated and fusiform. The growths varied from brownish red to bright red and were frequently associated with enlargement of the normal vessels of the cord. There was a general tendency toward increased vascularity of the associated structures, although an occasional case was encountered in which the absence of vascularity of the growth itself belied the angiomatous character of the tumor. Almost all the tumors were fairly firm to palpation and practically all were well encapsulated.

Microscopically, there was a fairly marked similarity in the essential structure of the tumors of this group. The parenchyma was composed of a tangle of newly formed capillaries lined by typical endothelial cells, which in some instances appeared swollen and vesicular (fig. 4 *a*). In most cases the capillaries could be seen to contain only a few erythrocytes, and many were empty; but in a few instances the channels were swollen and packed with erythrocytes and there were considerable hemorrhage and extravasated blood. The intercapillary cells contained, for the most part, abundant cytoplasm and moderate-sized, vesicular nuclei with chromophilic nuclear material. Occasionally, the cytoplasm was found to be vacuolated, but foci of "foam cells" were relatively few as compared with tumors of the following group. In several instances the tumor was seen to contain numerous, large, multinucleated cells with abundant cytoplasm and irregular, compact, bizarre-shaped nuclei, not unlike those encountered in some of the malignant gliomas. No evidence of malignant change was found in any of these tumors, and the formation of these giant cells was considered a retrogressive, rather than a progressive, change. Only occasional mitotic figures were observed.

Degenerative changes were found to some degree in practically all of the tumors, but in only about half was the process very extensive. In some instances large portions of the tumor tissue were highly edematous and there were cystlike spaces containing tumor tissue in various stages of granular degeneration. Hyalinization was frequently observed, and in several growths this had advanced to the stage in which practically all the tissue and channels were involved. Calcification, although occasionally observed, was not remarkable in any of the tumors. An occasional specimen stained for fat showed an abundance of this material scattered throughout the tissue in the form of small droplets (fig. 5 *a*). This appeared to be a degenerative product, different from the lipomatous tissue observed in the foregoing examples.

While all the tumors in this group were essentially capillary in type, all showed a certain compactness of structure which differentiated them

from the simple hemangiomas described in the first group. All the tumors were relatively cellular, and in almost all there were scattered regions in which the cellular elements predominated over the vascular. In all the tumors there was a network of reticulin, which was characteristic of the group (fig. 4 *b*).

The tumors in this group constitute one of the most commonly described types of vascular neoplasms encountered in the nervous system, particularly in the cerebellum. While characteristically neoplastic, it

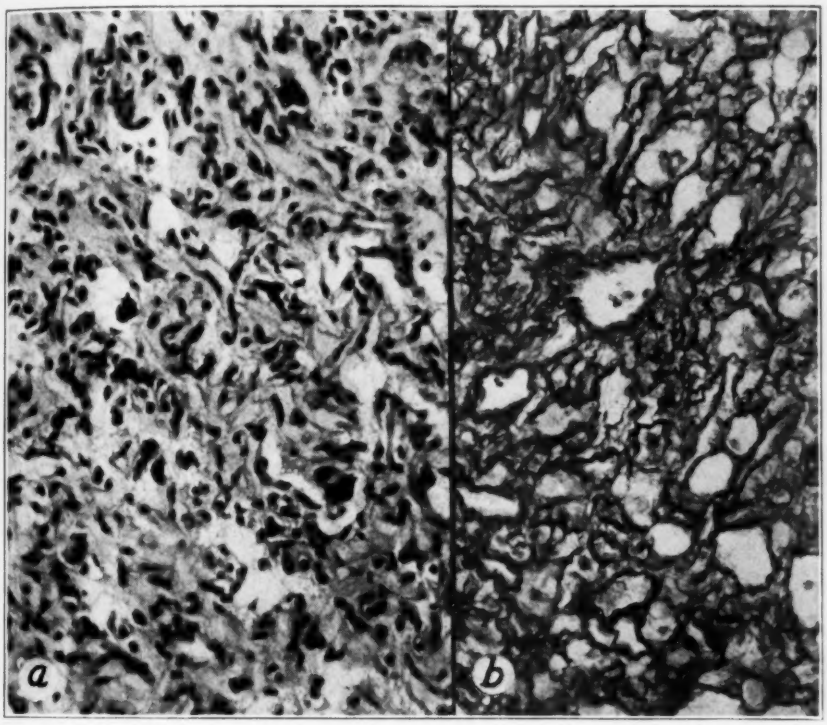

Fig. 4.—(*a*) Capillary hemangioendothelioma; note the tangle of newly formed capillaries and the presence of atypical multinucleated cells, the latter being interpreted as a retrogressive change; compare with figure 3 *a* (hematoxylin and eosin; × 285). (*b*) Perdrau stain, showing the characteristic reticulin; compare with figure 3 *b* (× 250).

represents an intermediate stage between tumors of the type first described and those in which proliferation of the endothelial cells has overshadowed the capillary nature of the growth. Of special interest is the advanced degree of degeneration which may take place in these and other vascular tumors. This is apparently dependent on the fact that despite the numerous potential vascular channels, the functional and the nutritional blood supply of the tumor is derived essentially from the

vessels associated with the supporting tissue. Indeed, buds of newly formed capillaries without lumens can be observed in many of the tumors, and in 1 of the intramedullary growths studied at necropsy such capillary buds, with and without lumens, could be observed projecting into the white matter of the cord.

Capillary Hemangioblastoma.—No typical example of capillary hemangioblastoma was encountered, although 2 tumors showed sufficient overgrowth of the cellular elements to justify inclusion in this group.

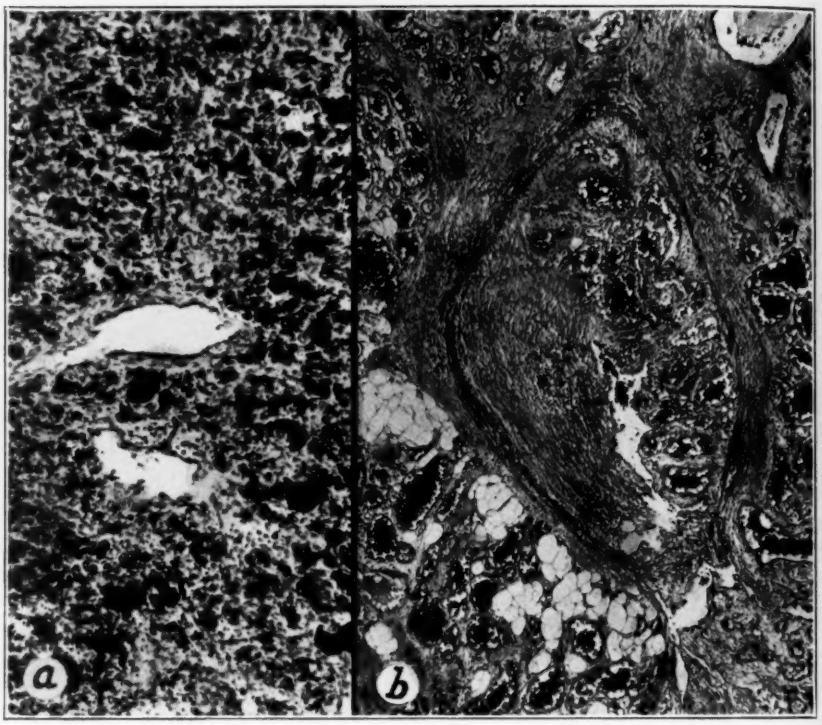

Fig. 5.—Retrogressive changes in vascular tumors. (*a*) Presence of intracellular lipoid distributed in droplets throughout a capillary hemangioendothelioma (Herxheimer stain; × 110). (*b*) Thrombosis and repair in a formed vessel in a mixed cavernous and capillary hemangioblastoma; note the similarity of the intravascular granulation tissue to the tumor tissue outside the vessel (hematoxylin and eosin; × 40).

In addition, several tumors included in the preceding group might possibly have been classified as mixed capillary hemangioblastoma and hemangioendothelioma. Both tumors referred to in the first sentence arose in the subdural space, 1 in the upper thoracic and the other in the lumbar region. Grossly, both tumors were large, and both were fairly well encapsulated. One was adherent to the filum terminale, as well

as to the adjacent arachnoid on the left anterolateral aspect of the cord, and the other was an unusually vascular tumor which had a pedicle presenting through the intervertebral foramen.

Microscopically, both growths were essentially capillary in architecture, but in both the proliferation of the intervascular tissue had progressed beyond the stage of the previous group. Each tumor possessed a well developed capsule, and in 1 instance this was completed by the presence of a subcapsular band of compressed tumor tissue. The two tumors differed in certain architectural features.

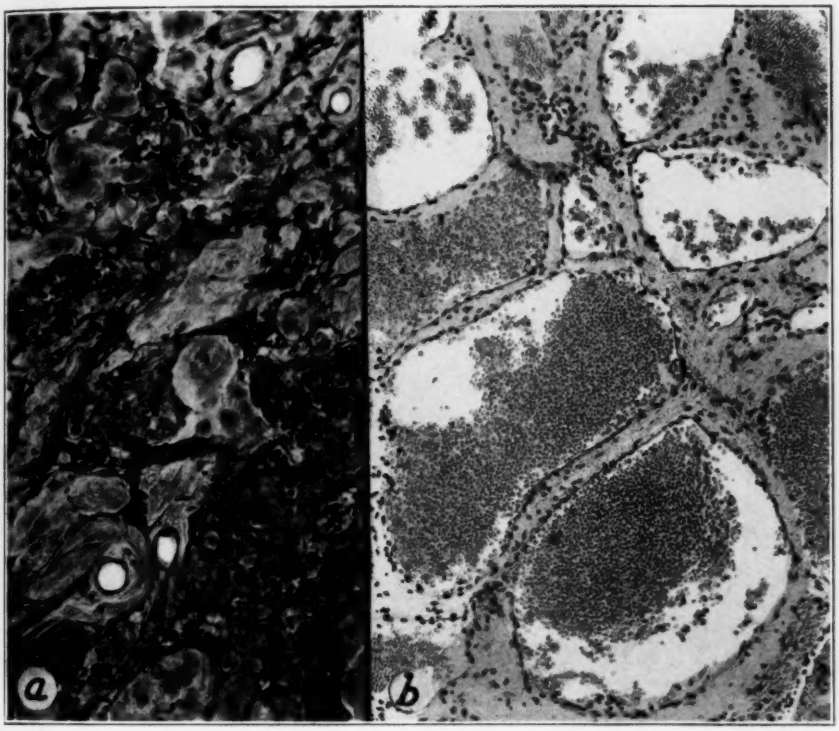

Fig. 6.—(*a*) Hemangioblastoma, with marked retrogressive changes in the form of extensive hyalinization; note the involvement of the vascular channels; compare with figure 7 *b* which is taken from the same tumor (hematoxylin and eosin; × 125). (*b*) Cavernous hemangioma, showing the simple structure of the tumor; the vascular channels are formed by flattened endothelial cells separated by narrow bands of connective tissue (hematoxylin and eosin; × 105).

One growth was highly cellular but was the seat of extensive retrogressive and degenerative changes which, for the most part, took the form of marked hyalinization (fig. 6 *a*). This involved the formed vessels as well as the neoplastic vascular channels, and in many places the tumor was reduced to coarse bands of hyalinized tissue with foci

of uninvolved tumor cells intervening. The intervascular tissue was in the form of columns and cords of cells, which contained slightly elongated or oval nuclei with chromophilic nuclear material. Pseudoxanthomatous cells were not prominent, and there were no regions of cystic degeneration. Mitotic figures were infrequently seen.

The second growth, while essentially capillary and cellular, contained typical large cavernous spaces lined by a single layer of endothelial cells, which lay on a thin band of supporting fibrous tissue. About the larger

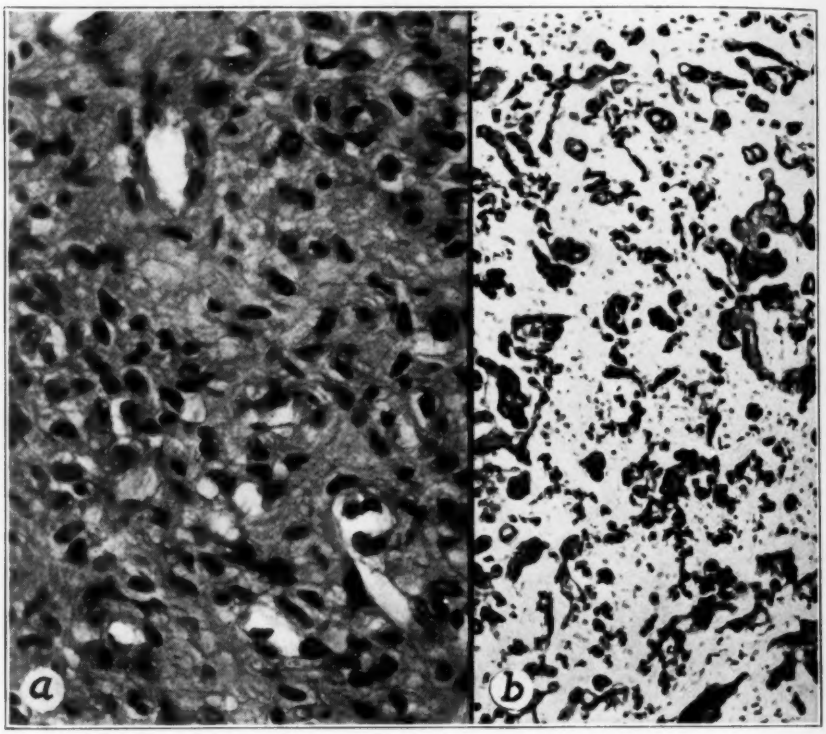

Fig. 7.—(*a*) Hemangioblastoma; note the highly cellular character of the tissue and the tendency toward vacuolation of the cytoplasm (hematoxylin and eosin; × 450). (*b*) Perdrau stain of a section from another hemangioblastoma which was the seat of extensive hyalinization; note the absence of reticulin and the manner in which the connective tissue is confined to the vascular channels (× 125).

vascular channels and cavernous sinuses characteristic cystic and granular degeneration could be seen frequently. The major portion of the tissue was composed of the usual newly formed capillary channels separated by columns of neoplastic cells (fig. 7 *a*). In only occasional places did the latter appear as "foam cells." In the essentially capillary regions the Perdrau stain revealed the characteristic fine reticulum, but in the more

cellular regions the intervascular reticulum was absent, except in the immediate vicinity of the larger blood spaces. Here, also, mitotic figures were identified only occasionally.

Hemangioblastoma, despite the degree of cellularity which may be present, must be considered as essentially a capillary tumor. The proliferation of intervascular tissue may in some instances be sufficient to alter the character of the tissue architecture (fig. 7 *b*), and in the early literature the vascular origin of these growths went unrecognized. Practically all these tumors contain a large amount of intracellular lipoid in the form of droplets, and Cushing and Bailey have noted the similarity of these lipoid-containing cells to those of hypernephroma and of the adrenal cortex.

Cavernous Hemangioma and Hemangioblastoma.—Nine tumors were microscopically cavernous in architecture. Because of the similarity between cavernous hemangioma and hemangioblastoma and because of the frequency with which intermediate forms are encountered, the two types will be considered together. Seven of the 9 tumors were situated extradurally, 1 was intramedullary and 1 was of pial origin, that is, extramedullary but subdural. One was encountered in the cervical region, and the remainder were from the thoracic region.

Grossly, the tumors were almost all fairly large and very vascular and frequently were associated with a plexiform mass of large vessels which were intimately related to the growth. They varied from brown through purplish red to bluish black, depending on the character of the associated vascular attachments. All were well encapsulated, and none showed invasion, although a few had caused erosion of the adjacent bony structures. The intramedullary tumor proved to be a well encapsulated, purplish red mass, which was situated in the thoracic region beneath the arachnoid.

Microscopically, although all the tumors were cavernous in architecture, all contained scattered regions which were of capillary structure, and there was a variable degree of cellularity of the intercavernous septums. In the more simple growths, the tissue consisted of numerous cavernous spaces lined by a single layer of flattened endothelium and separated by narrow bands of connective tissue (fig. 6 *b*). These tumors may be classified as cavernous hemangiomas; microscopically they showed little evidence of active growth. The cavernous spaces varied considerably in size, from those which appeared to be swollen and distended capillary channels to the large sinuses with poorly formed walls. Degenerative changes were commonly seen, and intercavernous edema and cystic degeneration often gave the tissue a more cellular appearance than was actually the case. In the more complex growths, the inter-

cavernous tissue was composed of columns and cords of cells not unlike those seen in hemangioendothelioma. With the Perdrau stain a reticulin, similar to that seen in capillary hemangioblastoma, was present in the intervening tissue. The degree of cellularity varied considerably in different tumors and in various parts of the same growth.

Degenerative and retrogressive changes were prominent in this group of tumors. Foci of calcification were evident in about half the growths. Hyalinization was present in many and extensive in several. Edema of the intercavernous tissue was present in almost every tumor and was pronounced in several. In the cavernous hemangiomas there was frequently moderate compression of the intercavernous tissue, and in the hemangioblastomas the cells often had less of the swollen appearance and often were somewhat elongated. This was particularly true at the periphery of the growth, where frequently the cavernous spaces were compressed to form elongated channels. Retrogressive changes, such as thrombosis and organization of vascular channels, were often seen in the central portion of the tumor, while progressive changes could be identified at the periphery (fig. 5 *b*).

Probably the greatest degree of architectural variation occurs in the cavernous type of vascular tumor, in which the intercavernous tissue may be composed of endothelial cells, capillary structures identical with those of the capillary hemangioendothelioma or simple collagenous connective tissue. In none of the examples studied was there any evidence of origin from a hamartomatous or congenital defect, nor was there any evidence of hemopoietic activity, as far as could be determined from the fixed specimen.

Hemangiosarcoma.—Five growths microscopically showed sufficient evidence of malignancy to be included in the group of sarcomas. Of these, 3 occurred in men and 2 in women. The age distribution of the patients ranged from 23 to 44 years. Three of the tumors were extradural, and 2 were of pial origin, being intradural but extramedullary. One was cervical, 2 were thoracic; 1 involved the lower thoracic and upper lumbar portions of the cord, and the remaining 1 was confined to the lumbar part of the canal.

The 5 tumors showed varying grades of malignancy and considerable difference in the architecture of the tissue, although all had certain characteristics apparently common to the sarcomas of vascular origin. In 2 instances there was gross evidence of invasion of the adjacent tissues, and in 1 case an extradural tumor had extended to involve the paravertebral muscles. In 2 cases in which the tumor occupied the region of the cauda equina there was involvement of the nerve roots.

Microscopically the angiomatous character of the 5 growths was evident, but in each certain changes in the character of the tissue had occurred which had altered the typical hemangiomatous architecture.

The least malignant of the group was an extradural tumor from the midthoracic region which had much the appearance of the usual capillary hemangioblastoma. However, there was a tendency for the cells, which varied considerably in size, shape and staining quality, to form small islands surrounded by vascular channels and a fine reticulin. Scattered throughout the tissue were giant cells in various stages of development. The Perdrau technic revealed a reticulum like that of the capillary hemangioblastoma.

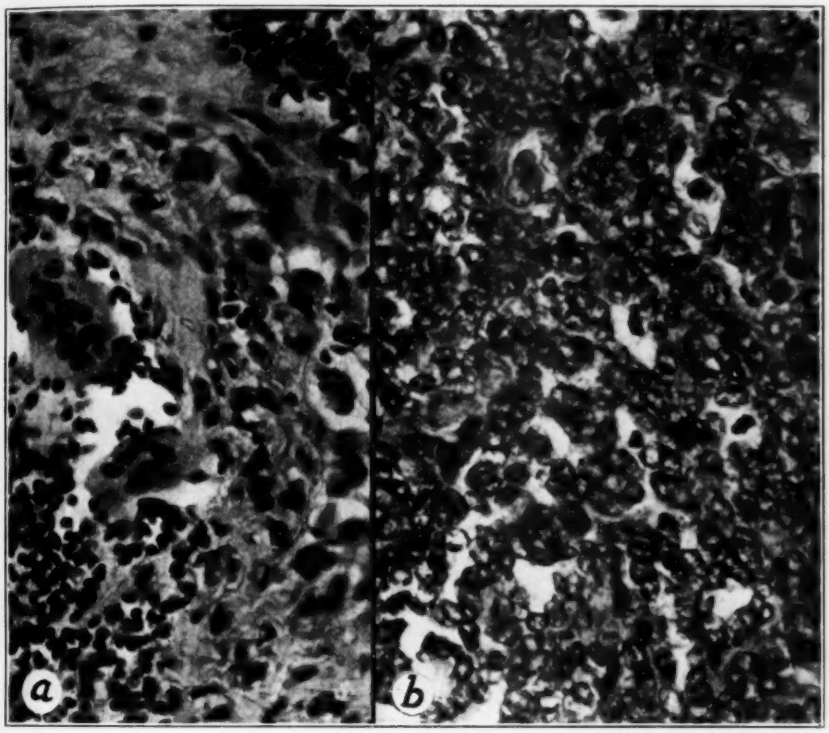

Fig. 8.—(*a*) Hemangiosarcoma; note the manner in which the neoplastic cells form the vascular channels, the invasion of the latter by tumor tissue and the presence of multinucleated giant cells and mitotic figures (hematoxylin and eosin; × 350). (*b*) Highly cellular and rapidly growing hemangiosarcoma; note the formation of the vascular spaces by the tumor cells and the abundance of mitotic figures (hematoxylin and eosin; × 450).

Two growths appeared to have advanced to a stage of malignancy just beyond that described in the preceding paragraph. Both were moderately cellular tumors containing numerous invasions of the blood spaces as well as of the supporting stroma (fig. 8 *a*). Both growths were extradural, and in 1 there was marked invasion of bone. Multinucleated giant cells were frequently encountered in both tumors, and a moderate

number of mitotic figures was present. One growth contained scattered foci of calcification. Degenerative changes were moderately advanced and varied from simple necrosis to an advanced degree of hyalinization. The tumor cells, in both instances, contained prominent nuclei which had a vesicular appearance, due to a fine chromatin network. In 1 growth the tumor cells had taken a characteristically sarcomatous appearance in places and were fusiform, with a distinct tendency toward streaming.

The most malignant-appearing tumor was a large growth removed from the intradural space in the lumbar region. The tissue was highly cellular and corresponded in architecture to hemangioblastoma. The individual cells, which varied considerably in size, contained large, oval nuclei with a prominent nuclear membrane and a moderate amount of poorly defined cytoplasm. Mitotic figures were numerous, and there was invasion of the supporting tissue as well as of the vascular channels (fig. 8 *b*). The latter, formed by the neoplastic cells, were frequently seen to contain tumor tissue in various stages of mitotic division and consisted for the most part of small capillary channels, which were overshadowed by the cellular overgrowth. Occasional large sinuses were seen. In some regions the typical capillary structure was clearly defined, but in others the cellular elements were present almost to the exclusion of the vascular components. There was little degeneration.

COMMENT

An attempt to classify the angiomatous growths of the nervous system as either true tumors (blastomatous lesions) or malformations (hamartomas) in a narrow sense may eventually prove to be misleading. Theoretically, at least, the two conceptions may be inclusive, since, although not necessarily recognizable in the fixed tissue preparation, a neoplastic growth may have had its origin in the confines of a malformation. One may assume that the force which initiates autonomous growth may work as well, or even more effectively, in hamartomatous tissue. In the present state of knowledge, however, one hesitates to agree fully with Bergstrand,[12] who stated that most, and perhaps all, of the true hemangiomas are malformations which have attained autonomous growth.

One of the outstanding features of the angiomas, arteriovenous or venous, is the mode of progression through enlargement of the individual vessels which go to form the tumor mass. This, in the strict sense of the word, cannot be called true growth but is enlargement dependent on static changes or changes in the dynamics of the blood circulating through

12. Bergstrand, H.: On the Classification of the Haemangiomatous Tumours and Malformations of the Central Nervous system, Acta path. et microbiol. Scandinav., 1936, supp. 26, pp. 89-95.

an existing abnormality and changes secondary to the disturbed physiologic situation. Related factors, such as inflammatory processes, may also contribute. A significant differentiating feature between the hamartoma and the vascular blastomatous lesion is the presence of pathologically active tissue between the vascular channels. This, however, does not occur in every instance and is to be differentiated from the presence of nerve and glia tissue, which has been referred to earlier in the paper. As an example, the presence of overgrowth of the intervascular cellular tissue in the hemangioblastoma characterizes that tissue as neoplastic, but in no way does it preclude the possibility of origin from a hamartomatous lesion. The latter question, in most instances, cannot be settled at present.

In the present series, no example was encountered comparable to the angioglioma of Roussy and Oberling, a growth supposed to be a combination of angiomatous and gliomatous tumor tissue. The origin of this tumor, as has been pointed out by Lindau,[13] is relatively uncertain and in a great many of the described cases can be best explained on the basis of reactive gliosis about an angiomatous tumor. Bergstrand and his associates [14] have introduced the term angioreticuloma for the type of vascular tumor commonly referred to as hemangioblastoma. Because of the tendency to rather wide variation in the tissue architecture and the changes in the character of the stroma which often occur secondary to overgrowth of the cellular components, the classification given here seems preferable.

13. Lindau, A., in discussion on Bergstrand.[12]

14. Bergstrand, H.; Olivecrona, H., and Tönnis, W.: Gefässmissbildungen und Gefässgeschwülste des Gehirns, Leipzig, Georg Thieme, 1936. Bergstrand.[12]

PERIPHERAL NEUROPATHY

EVALUATION OF SENSORY FINDINGS

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It is possible to reproduce the picture of peripheral neuropathy by temporarily interrupting the blood supply to an extremity.[1] Sensory dissociation is a characteristic feature of both ischemic neuropathy and the peripheral neuropathy complicating alcoholism and other conditions associated with disturbed nutrition.[2] Light touch, position and vibration senses are affected earlier and more severely, while pain sense appears to be relatively well preserved. Painful stimuli may, however, result in extremely unpleasant sensations. Such a sensation is best elicited by scraping the sole of the foot with an object such as a key, as in testing for the Babinski sign, and is experienced as "cutting" or "burning." This is an extremely unpleasant sensation, which in no way resembles tickling. Furthermore, this phenomenon does not occur in normal persons, and is invariably associated with defective sensation. For this reason, we have chosen to call it plantar dysesthesia, rather than hyperalgesia or hyperpathia.

Since the dysesthetic type of peripheral neuropathy predominantly affects the lower extremities, the response is usually elicited by stroking the sole of the foot. If, however, the condition has progressed to involve the upper extremities, the response may also be elicited by stroking the palm of the hand. The dysesthetic response may be almost

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1. Wortis, H.; Stein, M. H., and Jolliffe, N.: Fiber Dissociation in Peripheral Neuropathy, Arch. Int. Med., to be published.

2. Gowers, W. R.: A Manual of Diseases of the Nervous System, Philadelphia, P. Blakiston, Son & Co., 1888. Grinker, R. R.: Neurology, ed. 2, Springfield, Ill., Charles C. Thomas, Publisher, 1937. Wechsler, I. S.: A Textbook of Clinical Neurology, ed. 2, Philadelphia, W. B. Saunders Company, 1932. Brain, R.: Diseases of the Nervous System, London, Oxford University Press, 1933. Jolliffe, N.: Diagnosis, Treatment, and Prevention of Vitamin B_1 Deficiency, Bull. New York Acad. Med. **15**:469, 1939.

immediate or may be delayed to 2 seconds, and, as we shall indicate later, the presence of delay is related to the degree of involvement of the periphereal nerves.

Both sensory dissociation and dysesthesia have been associated with this syndrome for many years, but, beyond noting their presence, clinicians have been little concerned with the physiologic and metabolic importance of the phenomena. In this paper we attempt to make such a correlation.

The sensory peripheral nerve comprises three types of fibers, known as the A, B and C fibers, respectively.[3] These fibers differ in size, in irritability and in the speed at which impulses are transmitted (chart). It should be particularly noted that the small, unmyelinated C fibers transmit impulses at a rate far slower than the larger, myelinated A and B fibers. It was hoped that the various fiber types might be shown to serve specific sensory functions, but this expectation has been realized only to a limited extent.[4] It can be stated definitely that the fastest fibers convey touch and not pain impulses and that the slower C fibers transmit

*Fiber Types of Sensory Peripheral Nerves**

Type	Myelinated	Speed, Meters/Sec.	Threshold
A	Yes	30-75	1
B (or delta of A elevation)	Yes	15-25	10
C	No	1-2	100

* After Gasser.[5]

3. The terminology here presented is that given by Gasser in 1935 (A. Research Nerv. & Ment. Dis., Proc. [1934] **15**:35, 1935), and we have continued to use it throughout this paper for purposes of simplicity. Subsequently, however, Erlanger and Gasser (Electrical Signs of Nervous Activity, Philadelphia, University of Pennsylvania Press, 1937) preferred to consider the B elevation of the electroneurogram of the saphenous nerve as representing a subdivision (delta) of the A fibers. They confined the B elevation to the activity which appears in the fastest fibers in the gray rami and which does not occur in the sensory nerve. The A and C fibers mediate both sensory and motor activity (Grundfest, H.: Bioelectric Potentials, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Stanford University Press, 1940). In the latter classification, the B fibers are known to occur only in the preganglionic nerves of the autonomic nervous system and probably also in the postganglionic fibers of the ciliary nerve (Grundfest, H.: Properties of Mammalian B Fibers, Am. J. Physiol. **127**:252, 1939). An excellent experimental survey of this entire problem has recently been made by Zotterman (J. Physiol. **95**:1, 1939).

4. (*a*) Zotterman, Y.: Touch, Pain and Tickling, J. Physiol. **95**:1, 1939. (*b*) Gasser, H. S.: Control of Excitation in the Nervous System, in Harvey Lectures, 1936-1937, Baltimore, William & Wilkins Company, 1937.

pain impulses without those of touch or pressure. Touch, vibration and position sensory impulses are therefore carried by the faster A and B fibers, while pain impulses are carried by the intermediate B fibers and by the slower C fibers.[5] It is therefore clear that while, to a certain extent, fibers of different types carry different types of sensory impulses, those for pain are carried by two distinct groups of fibers. One group (B fibers) transmits impulses at the speed of 15 to 25 meters per second; the other (C fibers), at the rate of 1 to 2 meters per second.[6]

This quality of pain transmission has been employed by Lewis and Pochin [7] to explain the sensation of "double pain." Normally, a single pinprick of intermediate intensity applied to the skin of the distal portion of an extremity results in two sensations. The first is a discrete, not unpleasant, sense of sharpness, which is felt immediately after the stimulus is applied. The second is definitely unpleasant, more diffuse and prolonged. By the use of cocaine, which has been shown to block the C fibers first, the second response can be eliminated, while the first is still perceptible. On the other hand, local asphyxia blocks the faster A and B fibers first.[8] Here, the first response is eliminated, while the second is preserved. Furthermore, measurement of the delay in perception of the second (dysesthetic) response is found to be 2.0 seconds from the toe, 1.1 seconds from the knee and 0.8 second from the thigh.[7] This corresponds well to transmission of the dysesthetic painful sensation along the smaller C fibers, which, it will be recalled, transmit at the rate of 1 to 2 meters a second.

Furthermore, we have been able to produce a picture resembling peripheral neuropathy with plantar dysesthesia in normal persons by temporarily cutting off the blood supply to an extremity.[1] In this experiment, light touch, position and vibration sensations were affected earliest, indicating involvement of the A and B fibers. At this point the ankle jerk was diminished, and plantar dysesthesia of the immediate type became manifest. This, as will be seen, corresponds closely to the clinical picture seen in mild peripheral neuropathy. As the experiment continued, touch, position and vibration sensations were lost completely. The first pain response was lost, and plantar dysesthesia, although marked, was

5. Gasser, H. S.: Conduction in Nerves in Relation to Fiber Types, A. Research Nerv. & Ment. Dis., Proc. (1934) **15**:35, 1935.

6. Clark, D.; Hughes, J., and Gasser, H. S.: Afferent Function in the Group of Nerve Fibers of the Slowest Conduction Velocity, Am. J. Physiol. **114**:69, 1935. Gasser.[5]

7. Lewis, T., and Pochin, E. E.: The Double Pain Response of the Human Skin to a Single Stimulus, Clin. Sc. **3**:67, 1937.

8. Lewis, T., and Pochin, E. E.: The Effects of Asphyxia and Pressure on the Sensory Nerves of Man, Clin. Sc. **3**:141, 1938. Gasser.[5] Clark, Hughes and Gasser.[6]

perceived only after a noticeable delay of 1 to 2 seconds. This corresponds to a total blocking of the A and B fibers and indicates clearly that dysesthesia of the delayed type is conducted only by the slow, unmyelinated C fibers.

It thus becomes apparent that dysesthesia does not occur until some of the fast conducting (A and B) fibers have been blocked and that dysesthesia of the delayed type does not occur until practically all the faster A and B fibers have been blocked. Gasser [4b] suggested that the function of impulses which run on ahead of the others is to adjust the excitability of the synapse in preparation for later arrivals. Normally, the synapse is prepared by earlier arriving impulses, and the blow is cushioned. When the fast fibers are blocked, the force of the impulses transmitted by the slow fibers is allowed to pass undamped, and the result is a rush of unpleasant feelings, which may occur after a delay in perception. It seems plausible, therefore, to account for the dysesthesia which occurs in cases of peripheral neuropathy or of asphyxial block as the result of impulses traveling along more slowly conducting fibers and reaching synapses not properly blocked by faster traveling impulses. The uninhibited impulse is thus perceived at a much greater intensity than normal. This idea receives additional confirmation in a paper by Zotterman.[4a]

To illustrate further these principles as they apply to the peripheral neuropathy complicating chronic alcoholism and other conditions leading to disturbed nutrition, 2 cases are briefly presented.

REPORT OF CASES

CASE 1.—*Mild peripheral neuropathy in an alcohol addict.*

J. W., a Negress aged 29, was admitted to the medical service of the Psychiatric Division of Bellevue Hospital on Nov. 27, 1940, with a diagnosis of chronic alcoholism. She had been drinking heavily for a year or more and gave a history of dietary inadequacy.

Neurologic examination revealed evidences of mild peripheral neuropathy. The calf muscles were moderately tender and the ankle jerks absent. There was moderately severe plantar dysesthesia of the immediate type (perceived 0.4 second after the stimulus). The threshold for perception of pinprick was slightly higher than normal over the toes, but the stimulus was more unpleasant than over unaffected areas. There was slight impairment of touch and vibration sense over the distal portion of the foot. Position sense was questionably affected. There was no weakness. Examination of the upper extremities revealed no neurologic defects.

The fasting level of pyruvic acid in the blood was 1.45 mg. per hundred cubic centimeters (normal range, 0.77 to 1.16 mg.). This metabolic defect has been shown by Bueding and Wortis [9] to be a constant finding in cases of peripheral

9. Bueding, E., and Wortis, H.: Pyruvic Acid in the Blood and Cerebrospinal Fluid, Proc. Soc. Exper. Biol. & Med. **44**:245, 1940. Wortis, H., and Bueding, E.: The Clinical Significance of Pyruvic Acid in the Blood and Cerebrospinal Fluid, Tr. Am. Neurol. A. **90**:94, 1940.

neuropathy complicating alcoholism. After twelve days of treatment with thiamine hydrochloride all neurologic signs had returned to normal. Plantar dysesthesia and burning of the feet were no longer present.

CASE 2.—*Severe peripheral neuropathy in an alcohol addict with pronounced nutritional deficiency.*

H. G., aged 42, with chronic alcoholism and severe prolonged dietary insufficiency, was admitted to the medical service of the Psychiatric Division of Bellevue Hospital on Sept. 29, 1940. On admission, he showed moderate intellectual impairment, but was able to cooperate exceedingly well for examination. There was evidence of severe peripheral neuropathy with bilateral foot drop, complete areflexia and atrophy and tenderness of the calf muscles.

Of particular note was the presence of severe delayed plantar dysesthesia. The threshold was moderately high for perception of touch and pinprick, but even relatively light stroking of the sole caused a very unpleasant burning sensation, which was first perceived 2.0 seconds after the stimulus. Perception of pinprick was also delayed 2.0 seconds, and the sensation was burning and unpleasant.

Although the sensation of superficial pain was only moderately impaired, touch and vibration senses were markedly impaired below the knee. Position sense was absent in the toes but present in the ankles. There were sweating and cyanosis of both feet.

The upper extremities were similarly, but somewhat less severely, affected. There were bilateral wrist drop, areflexia and some wasting. When the palms of the hands were scraped with a blunt instrument, the patient complained of an unpleasant burning sensation, which was perceived without appreciable delay. Finger position, vibration and touch senses were severely impaired and pain sense moderately so.

Chemical examination of the blood revealed a fasting pyruvic acid level of 2.04 mg. per hundred cubic centimeters.

Treatment with large doses of preparations of the vitamin B complex resulted in progressive improvement. After a month, there was some return of position and vibration sense in the toes, tenderness of the calf muscles had entirely disappeared and plantar dysesthesia had markedly subsided. Pain could now be perceived immediately as a slight prick or scratch, but a crescendo of unpleasant feeling occurred 2 seconds after the stimulus.

In cases of mild peripheral neuropathy, therefore, as in case 1, the sensory changes, particularly the appearance of immediate dysesthesia and the moderate impairment of vibration and touch sensations, are similar to those which occur after a short period of local asphyxia. In these cases only part of the A and B fibers are affected. The severe form of the disease (case 2) resembles the state produced by prolonged asphyxia of the leg in the experimental subject. In the latter condition, dysesthesia is of the delayed type, vibration, touch and position senses are completely lost and pain sense is markedly impaired. In the severe form, all the A and B fibers have been blocked. The sensory changes are therefore more marked, and the dysesthesia is delayed.

COMMENT

Recent studies of fiber classification suggest that, in the peripheral nerve at least, the blocking of impulses which traverse the large, myelinated fibers allows the more unpleasant component of the double pain

complex to be perceived in an unmodified or uninhibited form.[4] It had been proposed originally by Head [10] that dysesthesia (or hyperpathia) occurring with lesions of the peripheral nerve might be the result of the removal of certain inhibitory impulses (associated with touch and discrimination), which allowed other impulses, unpleasant in character, to be perceived in uninhibited form. He applied a similar explanation to the dysesthetic phenomena occurring in the "thalamic syndrome," in which it was assumed that the thalamus was isolated from cortical inhibitory control.

Our clinical observations, furthermore, suggest that in the peripheral neuropathy complicating alcoholism and other conditions associated with disturbed nutrition the larger, myelinated (A and B) fibers are more severely affected, while the slow, unmyelinated (C) fibers are spared. This is further confirmed by the pathologic studies of Greenfield and Carmichael.[11] They studied the diseased peripheral nerves of alcohol addicts and of patients with subacute combined degeneration and found that in both groups the larger fibers were reduced in ratio and in number, as compared with those of controls. Swank [12] came to similar conclusions as a result of his observations on thiamine-deficient birds.

SUMMARY AND CONCLUSIONS

1. Sensory dissociation is a characteristic feature of the peripheral neuropathy complicating alcoholism and other conditions associated with disturbed nutrition. Light touch, vibration and position senses and "first" pain sense are affected earliest and most severely. These sensations are carried by the large, myelinated A and B fibers, which are affected earliest and most severely in such conditions. "Second" pain sense, which is conveyed along the slow, unmyelinated C fibers, is spared.

2. Immediate dysesthesia represents a stage of injury of the peripheral nerve at which some of the myelinated (A and B) fibers are still functioning, while others have been blocked.

3. Delayed dysesthesia represents the stage at which practically all of the myelinated (A and B) fibers have been blocked, only small, unmyelinated fibers continuing to function. The delay in perception results from the very slow transmission along the C fibers.

4. The sensory dissociation and dysesthesia of peripheral neuropathy may be duplicated experimentally by producing ischemia of an extremity.

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10. Head, H.: Studies in Neurology, London, Oxford University Press, 1920, vol. 2.

11. Greenfield, H. G., and Carmichael, E. A.: The Peripheral Nerves in Cases of Subacute Combined Degeneration of the Cord, Brain **58**:483, 1935.

12. Swank, R. L.: Avian Thiamin Deficiency, J. Exper. Med. **71**:683, 1940; personal communication to the author, 1940.

As the ischemia progresses, the loss of function of the peripheral nerve becomes more severe and the dysesthesia changes from the immediate to the delayed type.

5. In peripheral neuropathy of this type, the large, myelinated (A and B) fibers are primarily affected. This indicates that these fibers have greater metabolic needs, and are therefore most susceptible to nutritional deficiency.

TABES DORSALIS

EVALUATION OF THE SENSORY FINDINGS

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We have previously described the significance of the sensory dissociation and delay in pain perception which are associated with the peripheral neuropathy of chronic alcoholism,[1] and of a similar picture produced by temporarily interrupting the blood supply to an extremity.[2] It was observed that modalities which are eventually to be carried in the posterior columns and which are of more recent development in the phylogenetic scale are more likely to be impaired earlier and more severely. Light touch, vibration and position senses suffer most, while pain sense is fairly well preserved or, more commonly, preserved in a dysesthetic hyperpathic fashion. This picture is the result of the blocking of impulses which normally traverse the larger, myelinated nerve fibers, with preservation of the continuity of those impulses which are transmitted by the slower, unmyelinated fibers.

A similar sensory dissociation, delay in pain perception and dysesthesia are also noted in cases of tabes dorsalis. Involvement of those modalities known to be carried in the posterior columns (touch, position and vibration senses) is characteristically associated with this disease. The delay in pain perception and the dysesthesia are, however, not well recognized clinically, and the physiologic significance of these phenomena is not widely comprehended. Wilson,[3] in describing the sensory changes associated with tabes, noted that the pain which is felt after a delay of a second or two is sometimes of a peculiarly explosive or hyperpathic type. This dysesthesia is best elicited by stimulating the sole of the foot, as in

From the Neuropsychiatric Service of the Third (New York University) Division of Welfare Hospital, the Medical Service of the Psychiatric Division, Bellevue Hospital, and the Departments of Psychiatry and Medicine, New York University College of Medicine.

1. Stein, M. H.; Wortis, H., and Jolliffe, N.: Peripheral Neuropathy: Evaluation of the Sensory Findings, Arch. Neurol. & Psychiat., this issue, p. 464.

2. Wortis, H.; Stein, M. H., and Jolliffe, N.: Fiber Dissociation in Peripheral Neuropathy, Arch. Int. Med., to be published.

3. Wilson, S. A. K.: Neurology, Baltimore, Williams & Wilkins Company, 1940.

testing for the Babinski sign. We must emphasize that this experience in no way resembles the usual tickling sensation in normal persons. It is an exceedingly unpleasant burning pain and is invariably associated with a defect in sensation. The response may be immediate or may be delayed for 1 to 2 seconds.

As noted previously,[4] we have explained the sensory findings in cases of peripheral neuropathy on the basis of differential fiber transmission. It is our purpose in this paper to extend this interpretation to the sensory findings in cases of tabes dorsalis.

The theoretic background for this work has been established by the modern school of neurophysiology.[5] The results indicate that the peripheral nerve is composed of groups of fibers which differ in their fundamental characteristics (table 1). An inspection of the table reveals

TABLE 1.—*Fiber Types of the Sensory Peripheral Nerve* *

Fiber Type	Occurrence	Myelinated	Diameter, Microns	Speed of Transmission, Meters per Second	Modalities Transmitted	Order of Susceptibility to Lack of Oxygen
A (alpha) (beta) (gamma)	Motor and sensory nerves	Yes	Over 10	30-80	Vibration, Position, Light touch, First pain	2
(delta)	Motor and sensory nerve	Yes	5.5-9	8-30		1
B	Sympathetic gray rami (do not occur in peripheral nerve)	No	....	10	.....	?
C	Motor and sensory	No	Less than 5.5	1-2 (extremes) 0.5-5	Second pain	3

* After Gasser, Zotterman and others.[5]

that touch, position and vibration sensory impulses are carried by the myelinated fibers of relatively large diameter and high speed of transmission.[6] Furthermore, the fibers transmitting these impulses are most

4. Stein, Wortis and Jolliffe.[1] Wortis, Stein and Jolliffe.[2]

5. (*a*) Gasser, H. S.: Conduction in Nerves in Relation to Fibre Types, A. Research Nerv. & Ment. Dis., Proc. (1934) **14**:35, 1935. (*b*) Erlanger, J., and Gasser, H. S.: Electrical Signs of Nervous Activity, Philadelphia, University of Pennsylvania Press, 1937. (*c*) Grundfest, H.: Bioelectric Potentials, in Luck, J. M., and Hall, V. E.: Annual Review of Physiology, Stanford University, Calif., Stanford University Press, 1940, vol. 2, p. 213. (*d*) Properties of Mammalian B Fibers, Am. J. Physiol. **127**:252, 1939. (*e*) Zotterman, Y.: Touch, Pain and Tickling, J. Physiol. **95**:1, 1939. (*f*) Gasser, H. S.: Control of Excitation in the Nervous System, in Harvey Lectures, 1936-1937, Baltimore, Williams & Wilkins Company, 1937, p. 169. (*g*) Clark, D.; Hughes, J., and Gasser, H. S.: Afferent Function in the Group of Nerve Fibres of the Slowest Conduction Velocity, Am. J. Physiol. **114**:69, 1935.

6. Gasser.[5a] Zotterman.[5e]

susceptible to lack of oxygen.[7] On the other hand, pain impulses are transmitted by two sets of fibers. The larger fibers convey these impulses at the rate of 8 to 30 meters per second.[5e] Hence, a painful stimulus applied to the toe and transmitted along the A fibers would require not more than 0.03 to 0.12 second to reach the spinal cord. A similar impulse traversing the C fibers would, however, require 0.5 to 1 second to reach a similar destination. It is therefore logical to expect that an impulse which is transmitted by the slower, nonmyelinated fibers would be perceived later, even though its anatomic pathway to consciousness were the same. As a matter of fact, a pinprick of moderate intensity applied to the skin of the extremities does result in two sensations. The first sensation (carried along the fast A fibers) can be detected almost immediately after the stimulus as a localized, distinct, not very unpleasant prick. The second sensation (carried along the slow C fibers) is more diffuse and, if the stimulus is at all intense, is unpleasant and somewhat prolonged.[8] Lewis and Pochin [7a] have shown that by interrupting the blood supply to an extremity the first pain could be eliminated while the second was still preserved. At this point a painful stimulus was perceived only after a definite delay. We have confirmed this observation and have noted that light touch, position and vibration senses are markedly involved when this stage of anoxia of the peripheral nerves is reached.[2]

It has been pointed out by Pochin [9] that the delay in pain perception of tabetic persons approximates closely that which has been determined for "second" pain transmission in normal persons. He noted that 8 out of 12 of his tabetic patients showed a delay of 2 seconds in pain perception when the stimulus was applied to the toe. When applied to the knee, only 1 second was required to perceive the stimulus. In normal persons only a fraction of a second was necessary. This indicates that the delay in pain perception commonly observed in tabetic patients is due to blocking of those pain impulses which ordinarily traverse the faster, myelinated fibers and a preservation of pain conduction along the slow, unmyelinated C fibers.

RESULTS

Eighteen patients with sensory changes characteristic of tabes dorsalis were studied (table 2). In each there was complete areflexia of the lower extremities. Touch, position and vibration senses were

7. (*a*) Lewis, T., and Pochin, E. E.: The Effects of Asphyxia and Pressure on the Sensory Nerves of Man, Clin. Sc. **3**:141, 1938. (*b*) Wortis, Stein and Jolliffe.[2] (*c*) Gasser.[5a] (*d*) Clark, Hughes and Gasser.[5g]

8. Lewis, T., and Pochin, E. E.: The Double Pain Response of the Human Skin to a Single Stimulus, Clin. Sc. **3**:67, 1937.

9. Pochin, E. E.: Delay of Pain Perception in Tabes Dorsalis, Clin. Sc. **3**: 191, 1937.

involved, and pain was perceived in dysesthetic fashion. In 7 patients the dysesthetic response was immediate, while in 11 this response was obtained only after a perceptible delay. The response was elicited both by pinprick and by stimulation of the sole of the foot.

TABLE 2.—*Summary of Clinical Findings in Eighteen Patients with Tabes Dorsalis* *

Case No.	Sex	Age, Years	Duration of Symptoms, Years	Wassermann Reaction of Blood	Wassermann Reaction of Spinal Fluid	Plantar Dysesthesia †	Delay in Pain Perception, Sec.‡	Superficial Pain §	Touch §	Joint Position §	Vibration §	Deep Pain §	Reflexes ‖	Root Pain ¶	Comment; Description of Dysesthetic Sensation
1	F	79	30	—	—	4	2	0	2	4	3	0	a	0	"Burning"
2	F	49	10	+	+	4	1?	0	2	4	3	4	a	4	Delay uncertain because of patient's refusal to have stimulus repeated
3	M	61	9	+	—	3	1.5	2	2	4	2	4	a	2	Occasionally felt pinprick in 0.5 sec.; pain in 1.5 sec.
4	M	52	5	—	—	3	1.9	0	2	4	2	4	a	3	"Like a scratch"; electrical reactions normal
5	M	67	21	—	—	3	0	2	2	4	3	1	a	1	"Like something cold"
6	M	63	28	—	—	4	1.5	3	3	4	4	4	a	1	Hyperesthesia to cold; electrical reactions normal
7	M	55	3	+	+	2	0	2	2	3	3	3	a	1	
8	F	51	7	—	—	4	1.5	0	2	3	2	2	a	0	
9	M	71	12	—	..	4	2	0	2	3	3	4	a	0	"Like something hot"
10	M	55	3	+	+	4	1.5	2	1	4	3	4	a	2	
11	M	48	3	+	—	1	0	0	1	4	4	3	a	2	Dysesthesia to cold stimuli
12	F	47	6	—	—	3	1.5	0	2	4	2	1	a	2	
13	M	70	25	+	—	2	0	0	0	1	1	3	a	2	"Like a nasty feeling"
14	M	46	1	+	—	2	0	0	1	3	1	4	a	0	"Burning"
15	F	54	5	+	+	4	1.5	0	2	2	1	4	a	1	
16	M	58	11	+	+	2	0	0	1	4	3	4	a	2	"Burning"
17	M	63	6	..	..	2	1	1	0	3	2	4	a	2	Crescendo response to painful stimuli
18	M	64	26	+	—	4	1.5	3	2	4	4	2	a	3	"Burning"

* The ordinary clinical procedures were used in evaluating the neurologic status.

† 4 indicates a reaction of great intensity, the patient complaining of very severe pain; 1 indicates a relatively slight response.

‡ Delay was measured approximately by having the patient signal the examiner at the moment when the painful sensation was perceived. Values under 0.6 second were considered normal and are recorded as 0.

§ In evaluation of sensory modalities, 4 indicates a very severe defect; 0 indicates no, or very little, loss.

‖ Here, a indicates complete absence of knee and ankle jerks.

¶ 4 indicates very severe spontaneous root pain; 1 indicates slight or occasional root pain.

In our study of peripheral neuropathy,[1] we established the fact that immediate dysesthesia was associated with a lesser injury to the peripheral nerves in which only some of the large myelinated fibers had been blocked, and that delayed dysesthesia represented a more advanced stage of the disease in which practically all of the large, myelinated fibers

had been blocked. An attempt to establish a similar correlation between the severity of the disease and the presence of delayed dysesthesia in tabetic persons has not been as uniformly successful, but such a relation is suggested (table 2). It should also be noted that the severity of the dysesthetic response is not associated with the activity of the process.

COMMENT

We have previously noted that dysesthesia and delay in pain perception accompany the sensory dissociation seen with disturbances of function of the peripheral nerves.[4] Head [10] originally suggested that the epicritic sensory impulses exerted an inhibitory influence on the protopathic sensory impulses and that elimination of the former resulted in exaggeration of pain perception. The epicritic group corresponds roughly to those modalities which are known to be carried by the faster A fibers, while the protopathic group, again, corresponds in a general way to those carried by the slower fibers. "It is quite possible that the function of impulses which run on ahead of the others is to adjust the excitability of the synapse, in preparation for the arrival of later impulses [Gasser [5f]]." Head's idea of inhibition thus seems to have found neurophysiologic confirmation.

In cases of tabes dorsalis a similar sensory dissociation and delay in pain perception with dysesthesia are frequently seen. Here, however, the site of the anatomic and physiologic block is somewhere between the dorsal root ganglia and the spinal cord. Foerster,[11] in 1927, suggested that the fibers of the dorsal column of the spinal cord exert an inhibitory action on the central effect of the impulses carried in the lateral spinothalamic tract. He noted that isolated lesions of the dorsal column lead to "sensory hyperalgesia," which he interpreted as being a consequence of the blocking of the long ascending dorsal tracts (*ein Ausfallsymptom*). Zotterman,[5e] in commenting on Foerster's work, expressed a similar belief. "This sensory defect results from the exclusion of the highly differentiated and phylogenetically younger system of cutaneous sensory fibers, which normally exert an inhibitory influence upon the very ancient system of pain fibers." He pointed out that fibers within the spinal cord vary considerably in size and presumably in speed of transmission. The posterior columns are composed of fibers which are relatively large and fast conducting, while those composing the spinothalamic tracts are relatively small and slow conducting. It is thus probable at any rate that the transmission of impulses at different

10. Head, H., and others: Studies in Neurology, London, Oxford University Press, 1920, vol. 2.

11. Foerster, O.: Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände, Berlin, Urban & Schwarzenberg, 1927.

rates of speed occurs not only in the peripheral nerve but in the spinal cord. It is likely, furthermore, that the principle of inhibition of slowly conducting fibers by fast conducting ones also applies in the spinal cord. This suggests that a similar mechanism may be present throughout the nervous system. Kendall,[12] for example, reported 3 cases of disease affecting the brain stem in which both dysesthesia and delay in pain perception were present. The delay in each case was of the same order of magnitude as would be expected if there were a selective sparing of impulses conducted along the slow, unmyelinated C fibers. He, too, suggested that elimination of the larger, faster conducting impulses results in the reception of the slow impulses in an uninhibited fashion, with resultant dysesthesia.

Finally, the condition most commonly associated with dysesthetic manifestations is the "thalamic syndrome." Head[10] originally suggested that the apparent accentuation of painful sensations experienced by persons with this syndrome was the result of the removal of descending corticothalamic impulses, which are normally inhibitory and reduce the intensity of the ascending spinothalamic impulses. In his descriptions, delay is not mentioned as such, but some of his excellent case reports indicate that it did occur. It seems likely to us that some mechanism is at play similar to that described here.

CONCLUSIONS

1. Sensory dissociation and dysesthesia were noted in 18 patients with tabes dorsalis. In 11 of these patients the dysesthesia was delayed, and in each of these there was marked delay in pain perception.

2. The delay in pain perception and the dysesthesia have been related to blocking of fast conducting impulses, allowing more slowly conducted impulses to be perceived at a later time and in uninhibited fashion.

3. It is suggested that the physiologic mechanism of the delayed pain perception and dysesthesia associated with tabes dorsalis is analogous to that previously noted with disorders of the peripheral nerve.

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12. Kendall, D.: Some Observations on Central Pain, Brain **62**:253, 1939.

CHANGES IN THE BRAIN IN PERTUSSIS WITH CONVULSIONS

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The occurrence of neurologic complications in the course of pertussis has been recognized in the second half of the past century. The symptomatology and the gravity of prognosis of these complications in young children have been largely agreed on.

The study of pathologic changes in the brain in cases of pertussis with cerebral complications began essentially in the early part of this century. Various changes have been described by a number of authors, who gave different interpretations of the relation of the cerebral lesions to the pathogenesis of these complications. In some cases no pathologic changes were observed in the brain (Ford,[1] in 5 of 11 cases; Grenet and Mourrut,[2] in 12 of 15 cases).

REVIEW OF LITERATURE

The changes observed by the various authors may be classified roughly into three groups: (*a*) circulatory, (*b*) degenerative and (*c*) inflammatory.

Circulatory Changes.—These include hemorrhages, vascular spasm and edema.

Hemorrhages: Multiple small hemorrhages scattered throughout the brain were described by a number of early observers, in most cases on gross examination. Lately many authors have tended to dismiss as unimportant the presence of scattered cerebral hemorrhages in cases of pertussis with cerebral manifestations, either because they failed to observe them in their cases or because such hemorrhages occur in other diseases as well. Of recent authors, Ford observed multiple small hemorrhages as the only pathologic change in 3 of his 11 cases. Singer[3] saw small hemorrhages, often associated with degenerative cellular changes, in a number of his cases. He expressed the opinion that the hemorrhages were an essential part of the pathologic changes in the

From the Pathologic Laboratories of the Willard Parker Hospital.

1. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, Springfield, Ill., Charles C. Thomas, Publisher, 1937.

2. Grenet, H., and Mourrut, E.: Les convulsions de la coqueluche, Bull. Soc. de pédiat. de Paris **31**:233, 1933.

3. Singer, L.: Ueber die Keuchhustenapoplexie, Ztschr. f. Kreislaufforsch. **20**:338, 1928.

brain in pertussis. Several authors who diagnosed the condition in their cases as encephalitis observed multiple small hemorrhages in the brain.

The rare occurrence of massive cerebral hemorrhages is generally recognized. A few cases in which hemiplegia occurred during pertussis in older children, with partial or complete recovery, have been described in the literature. A massive hemorrhage into the white matter of the brain in an infant was reported by Singer.

Massive hemorrhages into the meninges are a more frequent postmortem observation than massive cerebral hemorrhages (cases of Hada,[4] Cannelli,[5] Ford [1] and others).

Vascular Spasm: Singer [6] and other authors asserted that vascular spasm of vasomotor origin, although not demonstrable at autopsy, is the most important pathophysiologic process leading to stasis, diapedesis, hemorrhages and anoxemic changes in the brain. Hiller and Grinker,[7] in describing a case of cerebral softening occurring in pertussis, explained its origin on the basis of functional circulatory disturbance.

Edema: Habel and Lucchesi [8] stated that edema, especially cellular edema, resulting from vasomotor disturbances and anoxemia, is the cause of convulsions in pertussis.

Degenerative Changes.—Husler and Spatz [9] were the first to describe degenerative cellular changes in the brain in cases of pertussis with convulsions. They observed that the cells of the superficial layers of the cortex, of the striate body, of the hippocampus and of the cerebellum (the Purkinje cells and the cells of the dentate nucleus) stained deeply with eosin and lost the ability to stain with basic aniline stains. The changes were of the kind which are encountered in ischemic areas and which Spielmeyer [10] occasionally observed in the Purkinje cells in association with several infectious diseases; in the latter cells Spielmeyer observed complete loss of staining with aniline dyes and called it

4. Hada, B.: Ueber die Gehirnkomplikationen des Keuchhustens mit besonderer Berücksichtigung der Pachymeningitis productiva interna, Virchows Arch. f. path. Anat. **214**:206, 1913.

5. Cannelli, A. F.: Contributo allo studio delle complicazioni meningee emorragiche da pertosse, Pediatria **27**:351, 1919.

6. Singer, L.: (*a*) Zur Pathogenese der Keuchhustenapoplexie und Keuchhusteneklampsie, Virchows Arch. f. path. Anat. **274**:645, 1929; (*b*) footnote 3.

7. Hiller, F., and Grinker, R. R.: Functional Circulatory Disturbances and Organic Obstruction of the Cerebral Blood Vessels, with a Contribution to the Pathology of Pertussis Eclampsia, Arch. Neurol. & Psychiat. **23**:634 (April) 1930.

8. Habel, K., and Lucchesi, P. F.: Convulsions Complicating Pertussis, Am. J. Dis. Child. **56**:275 (Aug.) 1938.

9. Husler, J., and Spatz, H.: Die "Keuchhusten-Eklampsie," Ztschr. f. Kinderh. **38**:428, 1924.

10. Spielmeyer, W.: Ueber einige Beziehungen zwischen Ganglienzellenveränderungen und gliösen Erscheinungen, besonders am Kleinhirn, Ztschr. f. d. ges. Neurol. u. Psychiat. **54**:1, 1920.

"homogenizing degeneration." Husler and Spatz emphasized the degenerative character of such lesions and pointed out that encephalitis was not present. Their observations were soon corroborated by Neubürger [11] and by Jochims [12]; the latter introduced the term "pertussis encephalopathy" to describe these degenerative changes of probable toxic origin. Yamaoka,[13] Ford,[1] Dubois, Ley and Dagnelie [14] and Singer found changes identical with those described by Husler and Spatz.

Inflammatory Changes.—These include meningitis and encephalitis.

Meningitis: This condition has been observed by several authors, who attribute a varying degree of importance to its occurrence. Neurath [15] observed rather mild meningitis in most of his 25 cases and concluded that it was the cause of cerebral manifestations. It must be noted that in several of his patients pertussis was combined with pulmonary tuberculosis, scarlet fever, measles or varicella. Husler and Spatz found a slight meningitis in their 2 cases, but concluded that it was of less significance than the cellular changes associated with pertussis. Dubois, Ley and Dagnelie observed lymphocytic meningitis in 5 of their 7 cases, like the two preceding authors, concluded that the degenerative cellular changes were more characteristic of the cerebral pathology of pertussis with convulsions.

Encephalitis: In reviewing the cases to be classified pathologically as those of "encephalitis," one meets with considerable difficulty because of the difference in conceptions of what constitutes encephalitis. Many authors, in reviewing the literature on pertussis with neurologic manifestations, have classified the cases in which degenerative cellular changes appeared as instances of encephalitis. While Husler and Spatz and Dubois and associates emphasized that the changes they observed were not inflammatory, their cases are repeatedly referred to by reviewers as instances of encephalitis. It would be best, therefore, to include in this section the cases in which the respective authors themselves called the cerebral complication encephalitis.

Askin and Zimmerman [16] described a case in which, in addition to a subarachnoid hemorrhage at the base of the brain, scattered collections

11. Neubürger, K.: Ueber die Pathogenese der Keuchhusteneklampsie, Klin. Wchnschr. **4**:113, 1925.

12. Jochims, J.: Ein Beitrag zur Keuchhusten-Encephalopathie, Ztschr. f. Kinderh. **45**:326, 1928.

13. Yamaoka, Y.: Studien über das Keuchhustengehirn: I. Histopathologische Studien über das menschliche Keuchhustengehirn, Ztschr. f. Kinderh. **47**:543, 1929.

14. Dubois, R.; Ley, R. A., and Dagnelie, J.: Contribution anatomo-clinique à l'étude des complications neurologiques et tout particulièrement des convulsions de la coqueluche, Rev. franç. de pédiat. **9**:49, 1933.

15. Neurath, R.: Die nervösen Komplikationen und Nachkrankheiten des Keuchhustens, Arb. a. d. neurol. Inst. a. d. Wien. Univ. **11**:258, 1904.

16. Askin, J. A., and Zimmerman, H. M.: Encephalitis Accompanying Whooping Cough, Am. J. Dis. Child. **38**:97 (July) 1929.

of mononuclear cells with deep-staining or vesicular nuclei were observed in the cerebral hemispheres, in the striate body and in the subependymal areas. No blood vessels were demonstrated within these cellular collections. The ganglion cells of the cortex and hippocampus stained normally.

Mourrut [17] presented a pathologic report of 3 cases, 2 of hemorrhagic and 1 of nonhemorrhagic encephalitis. In both cases in which hemorrhagic lesions were present measles developed during the course of pertussis, and these cases cannot therefore be considered clearcut instances of damage to the brain occurring in pertussis. In both cases perivascular demyelination was noted; in 1 of them the loss of myelin was limited to the areas infiltrated with blood. In the third case (that of a girl 7 years old) there were mononuclear meningitis and perivascular infiltrates in the rolandic cortex. No degeneration of nerve cells, no hemorrhage and no excessive congestion was noted.

Although they entitled their paper "Encephalopathy of Pertussis," Fattovich and Lenti [18] described the changes as "encephalitic" in the summary. They observed degenerative cellular changes, which apparently did not reach the stage of homogenization; numerous thrombi, mostly lymphocytic, and occasional mononuclear cells, which they considered to be lymphocytes, in the white matter bordering the capillaries.

Grenet and Mourrut [2] mentioned 3 cases of "congestive and hemorrhagic encephalitis," which they compared to "any secondary encephalitis of infancy."

Occasional perivascular cellular infiltrates in the brains of patients with pertussis were mentioned by several authors who did not call the condition encephalitis (Neurath, Habel and Lucchesi and others).

As is seen from the foregoing partial review of the literature, there is no uniformity of histologic changes in cases of pertussis with neurologic manifestations. The relative frequency of these changes is difficult to estimate from the extensive published material, for several reasons. First, in many cases reported pertussis occurred in combination with one or more infectious diseases; again, the approach of the older and that of the more recent observers are different, as a result of the relatively recent knowledge concerning the degenerative cellular changes in pertussis.

In a number of cases of pertussis with convulsions at the Willard Parker Hospital, autopsy presented the opportunity to evaluate the relative frequency of the pathologic changes in material worked up in a fairly uniform manner. The cases in which neurologic manifestations could be explained on a basis other than pertussis (e. g., a case of

17. Mourrut, E.: Les convulsions de la coqueluche, Thesis, Paris, 1933.

18. Fattovich, G., and Lenti, P.: Sulle cosidette encefalopatie da pertosse, Rassegna di studi psichiat. **27**:13, 1938.

pertussis combined with measles, a case of pertussis with miliary tuberculosis and tuberculous meningitis, a case of pertussis in a mentally deficient child with slight hydrocephalus) were not included in this series.

This study is based on pathologic material from 15 patients who had pertussis with convulsions (10 girls; 5 boys), none of whom was above 2 years of age.

The brains were fixed in a 4 or 6 per cent concentration of solution of formaldehyde U. S. P. or in Hortega's solution of formaldehyde with ammonium bromide. Blocks of tissue were taken from the motor and the frontal cortex, from the basal ganglia, from the hippocampus, from the cerebellum and from the medulla. In several cases sections were made also from the substantia nigra, from the optic nerves and from the spinal cord. In 4 cases from the files no sections from the hippocampus were available. The stains used routinely were hematoxylin and eosin (or hematoxylin and phloxine) and cresyl violet. The Masson stain (Goldner's modification), Mahon's myelin stain (King's modification [19]) and scarlet red, for fat, were employed when indicated.

REPORT OF CASES

CASE 1.—R. M., a 2 year old white girl, had generalized convulsions on the eighteenth day of paroxysmal cough. She was admitted to the hospital on that day, with cyanosis and generalized convulsions. The eyes deviated to the right; the pupils were dilated but reacted to light. The temperature was 107 F., the pulse rate 100 and the respiratory rate 25. Stimulants were given, followed by sedatives and a clysis of dextrose but the child did not respond to treatment and died four hours after admission.

The spinal fluid was clear; a few mononuclears were present in the smear.

Necropsy.—Brain: Gross examination: Congestion and edema were noted, and a few petechial hemorrhages were present in the white matter.

Microscopic examination: There were meningeal, pericellular and perivascular edema; mononuclear plugs in the meningeal veins and in the cerebral veins and capillaries; petechial hemorrhages in the floor of the fourth ventricle and "eosinophilic degeneration" of many pyramidal cells in the hippocampus and in the Purkinje cells (the latter being practically colorless in cresyl violet preparations).

Other Organs: Minimal pneumonia was superimposed on atelectasis. Some mucus was present in the right middle ear (Bacillus pyocyaneus). Lymphocytic plugs were noted in the epicardial veins and in a renal artery.

A culture of the brain was negative for Haemophilus pertussis.

Virus studies on the brain (Dr. Margaret Holden) gave negative results.

CASE 2.—C. G., a 6 month old white girl, was admitted to the hospital on the ninth day of illness, with pertussis and difficulties in feeding. She was afebrile. There were a few rales in the chest. The blood count showed 17,000 white cells, with 74 per cent lymphocytes. On the sixteenth day of illness the temperature began to rise. On the eighteenth day pneumonia was found, and vague neurologic signs were noted. On the nineteenth day long paroxysms of cough with cyanosis occurred. A carpopedal spasm developed; the serum calcium was 12 mg. per

19. King, L. S.: Personal communication to the author.

hundred cubic centimeters. The spinal fluid was blood tinged. On the twenty-second day of illness the spinal fluid contained 70 cells per cubic millimeter, 70 per cent polymorphonuclears, an increased amount of globulin and a few gram-negative structures suggestive of diplococci. Antimeningococcus serum was administered. The following day the spinal fluid contained 530 cells per cubic millimeter, with 85 per cent polymorphonuclears; the temperature rose to 105.8 F. The child died on the twenty-fifth day of illness.

Necropsy.—Brain: Gross examination: The brain weighed 645 Gm. The veins were congested, and a few thin adhesions were present at the base of the brain.

Microscopic examination: There were subarachnoid edema and small subarachnoid hemorrhages. Mononuclear phagocytes, lymphocytes and some polymorphonuclears were present near the hemorrhages and at the base of the brain. Wide perivascular spaces, with some red cells, occurred in the brain. Eosinophilic degeneration was present in many cortical cells, all the hippocampal pyramidal cells, most of the Purkinje cells and many cells of the basal ganglia. The hippocampal pyramidal cells stained diffusely dark with cresyl violet; most of the Purkinje cells were almost colorless. A number of rod-shaped glia cells were present in the cortex of the island of Reil.

Other Organs: Patchy pneumonia (pneumococcus type XX) was superimposed on atelectasis in both lungs.

Case 3.—E. C., a 13 month old white girl, was admitted to the hospital on the thirtieth day of pertussis, because of convulsions following a paroxysm of coughing. Spasticity of both left extremities was noted. A carpopedal spasm occurred. The knee jerks were exaggerated. The pupils were dilated and did not react to light. The temperature was 106 F., the pulse rate over 150 and the respiratory rate 60. The spinal fluid was blood tinged (traumatic?). The blood count showed 52,000 white cells, with 62 per cent lymphocytes. During the following days the neurologic signs changed from hour to hour. On the thirty-fifth day of illness the serum calcium was 6.2 mg. per hundred cubic centimeters; after intravenous administration of calcium gluconate the calcium level remained between 9.75 and 9.2 mg. The carbon dioxide–combining power was 29 per cent, but after the administration of alkali it rose to 48 per cent. Other medications included administration of 5 per cent dextrose in physiologic solution of sodium chloride. The patient showed no improvement—spasticity, increased reflexes and nuchal rigidity were present. Signs of incipient pulmonary consolidation appeared. The blood count showed 16,000 white cells, 63 per cent of which were lymphocytes. The patient died on the forty-fourth day of illness.

Necropsy.—Brain: Gross examination: Edema, a small subarachnoid extravasation of blood over the right precentral area and moderate congestion of the white matter of the brain were noted. The spinal cord was grossly normal.

Microscopic examination: There were diffuse congestion and pericellular and perivascular edema. Petechial hemorrhages were noted in the white matter of the hippocampus, in the floor and roof of the fourth ventricle, in the area of the inferior olives and in the anterior horn of the cervical portion of the cord. Eosinophilic degeneration was present in the pyramidal cells of the cortex, the hippocampus, the thalamus and the dentate nucleus and in the Purkinje cells; the Purkinje cells were colorless in cresyl violet preparations.

Other Organs: The right middle ear contained mucopurulent material, from which Pneumococcus type XXII and Staphylococcus aureus were cultured. The left middle ear was normal. Patchy pneumonia (Pneumococcus type XXII) was superimposed on extensive atelectasis.

CASE 4.—E. W., a 10 month old white girl, was admitted to the hospital on the thirtieth day of pertussis because of convulsions and hematemesis. On admission the child looked acutely ill, but the general physical and neurologic examinations revealed nothing abnormal. During the examination the child fell from the carriage to the floor, but aside from bleeding gums there was no other sign of trauma. The temperature was 100 F. The blood count showed 50,000 white cells, with 74 per cent lymphocytes. The spinal fluid was clear; the amount of protein was increased; the smear showed an increased number of mononuclear cells. Throughout the day the child had rhythmic twitchings of the face and of the left arm and hand. The temperature rose to 107 F., the pulse rate was 106 and the respiratory rate 70. Sedatives were given. Cheyne-Stokes respiration developed, and the patient became comatose. She died twenty-four hours after the onset of convulsions.

Necropsy.—There was no evidence of trauma of the skull.

Brain: Gross examination: The brain weighed 900 Gm. No hemorrhages were seen. A few nonadherent clots were present in the meningeal veins on the left side. Subarachnoid edema was marked.

Microscopic examination: Marked perivascular and moderate pericellular edema and small perivascular hemorrhages in the cortex, in the hippocampus and in the cervical portion of the cord were noted. Some hippocampal pyramidal cells and many Purkinje cells showed eosinophilic degeneration (the latter were almost colorless in cresyl violet sections). The glia cells in the white matter had undergone pericapillary marginal alinement, and a glial nodule occurred in the medulla. Only one lymphocytic plug, in a small vein, was noted.

Other Organs: The middle ears were clear. Soft postmortem clots in the venous sinuses were observed. Atelectasis and bronchitis were noted. The liver showed severe fatty replacement.

Culture of the brain was negative for H. pertussis.

CASE 5.—A. LaB., a 14 month old white girl, had convulsions on the twenty-second day of pertussis. When admitted to the hospital, on the twenty-fourth day of the disease, she did not appear to be severely ill. The temperature was 101 F., the pulse rate 160 and the respiratory rate 40. The blood count showed 85,000 white cells, with 58 per cent lymphocytes. The first day in the hospital generalized tonic convulsions developed during paroxysms of cough. The next day spastic twitchings developed over the entire body, and she ceased breathing; artificial respirations and stimulants were applied. After the attack reflexes were hyperactive and ankle clonus was present. On the twenty-sixth day of illness the temperature rose to 105 F. and occasional convulsions occurred. As there was a history of convulsions at the age of 5 weeks, which was relieved by administration of a calcium compound, and as the serum calcium was found to be 7.7 mg. per hundred cubic centimeters, the patient was given calcium gluconate; a carpopedal spasm developed, nevertheless. The patient died on the twenty-eighth day of illness.

Necropsy.—Brain: Gross examination: The meninges were not edematous; the meningeal blood vessels were congested, and a small extravasation of blood around the pons (resulting from a torn blood vessel during removal of the brain?) was noted. The terminal veins of the third ventricle were engorged. The fluid in the ventricles was clear.

Microscopic examination: There were small subarachnoid extravasations in the motor and hippocampal areas, a small number of red cells in the aqueduct and the fourth ventricle and petechiae in the roof of the fourth ventricle. A tear in a small artery at the base of the pons, probably a postmortem artefact, was noted.

(No degeneration of the arterial wall was apparent.) There was eosinophilic degeneration of some hippocampal pyramidal cells and of numerous Purkinje cells, and lymphocytic plugs were present in the meningeal and cerebral blood vessels.

Other Organs: Examination revealed bronchitis, but no pneumonia. Pneumococcus type IV and Haemophilus influenzae were isolated on culture of material from the lungs.

Culture of the brain was negative for H. pertussis.

Case 6.—F. S., an 8 month old white boy, was admitted to Bellevue Hospital on the eighth day of the cough. Shortly after admission the cough was noticed to be paroxysmal. Two blood counts showed 98,600 white cells, with 69 per cent lymphocytes, and 109,000 white cells, with 64 per cent lymphocytes, respectively. The diagnosis of pertussis was made, and the child was transferred to the Willard Parker Hospital on the tenth day of illness. He was dyspneic and cyanotic. The temperature was 103 F., the pulse rate 110 and the respiratory rate 50. Rales were present on both sides of the chest, but roentgen examination failed to show any pneumonia. The blood count revealed 61,000 white cells, with 70 per cent lymphocytes. The next day, during a transfusion, the child stopped breathing but was resuscitated by stimulants and artificial respiration. He subsequently had generalized convulsions, and generalized twitchings persisted through the next twenty-four hours. During the following week the temperature fluctuated at about 101 F. On the nineteenth day of illness the child again had generalized convulsions; the neurologic examination following the convulsions was negative. The spinal fluid was normal. The temperature during that day rose to 109 F. The child died the same day.

Necropsy.—Brain: Gross examination: Severe subarachnoid edema and congestion of meningeal veins were present.

Microscopic examination: Edema of the meninges; wide perivascular and pericellular spaces; lymphocytic plugs in the blood vessels of the meninges, brain and cerebellum, and eosinophilic degeneration of the pyramidal cells of the cortex and the dentate nucleus and of some Purkinje cells were noted. Completely homogenized Purkinje cells were seen rarely.

Other Organs: One microscopic area of pneumonia was noted. The middle ears and dural sinuses were normal.

Culture of the brain was negative for H. pertussis.

Case 7.—D. McP., a 9 month old white boy was admitted to the hospital on the fourteenth day of pertussis, with convulsions and abnormal rolling of the eyes. There was bilateral bronchopneumonia, a mucopurulent discharge from the nose and bilateral chronic otitis media. Later in the day the pupils were found to be widely dilated, and marked spasticity of both upper extremities and the right lower extremity was noted. The blood count showed 156,000 white cells, with 72 per cent lymphocytes. The spinal fluid contained 5 cells per cubic millimeter (polymorphonuclears). The next day the child became dyspneic and prostrate; the temperature was 108 F. On the sixteenth day of illness he vomited some "coffee grounds" material and died shortly thereafter.

Necropsy.—Brain: Gross examination: The brain weighed 1,050 Gm. Congestion of the meningeal capillaries, but no meningeal exudate, was noted.

Microscopic examination: There were observed meningeal edema; small subarachnoid extravasations of blood; slightly increased mononuclear cellularity of the meninges; lymphocytic plugs in a few meningeal veins; widening of perivascular and

pericellular spaces in the brain and medulla; small hemorrhages in the white matter of the cerebellum; eosinophilic degeneration of many Purkinje cells; small plugs consisting of lymphocytes, or of lymphocytes and polymorphonuclears, in the cortex, cerebellum and pons, and thrombi, with a considerable proportion of polymorphonuclears, in the striate body.

Other Organs: Examination revealed perforation in the lower portion of the esophagus; acute hemorrhagic mediastinitis of the posterior mediastinum; bronchopneumonia of the upper lobe of the right lung and the lower lobe of the left lung, and bilateral catarrhal otitis media, extending into the mastoids. The dura and the venous sinuses showed no pathologic change.

Conclusion.—The cerebral complications preceded death by several days. Perforation of the esophagus was a recent, terminal complication.

Case 8.—T. R. H., a 2 year old white girl had convulsions after a paroxysm of cough on the twenty-fourth day of pertussis. She was admitted to the hospital on the twenty-fifth day of illness, with a temperature of 106.5 F. and slight general spasticity, but no other neurologic signs. Crepitant rales were present throughout the chest. The spinal fluid was blood tinged. Later in the day there developed spastic convulsions with opisthotonos, lasting from a few minutes to three hours, during which the patient bit her tongue. Ankle clonus and a Babinski sign developed on the left side. The child died on the twenty-sixth day of pertussis.

Necropsy.—Brain: Gross examination: The brain weighed 1,140 Gm. The blood vessels of the meninges and the white matter were congested, but no gross hemorrhage was apparent.

Microscopic examination: There were observed edema of the meninges; rare small subarachnoid extravasations; slightly increased mononuclear cellularity of the meninges; small hemorrhages in the thalamus and in the white matter of the cerebelum; wide perivascular spaces with small perivascular extravasations in the striate body and in the white matter of the cerebral cortex; areas of état criblé in the white matter; calcium-like deposits in the walls of a few blood vessels of the striate body; minimal increase of fibroblasts in the adventitia of a few blood vessels in the striate body, and eosinophilic degeneration of some Purkinje cells and cortical pyramidal cells. Sections of the hippocampus were not available.

Other Organs: Patchy bronchopneumonia and atelectasis were present. The dural sinuses were normal.

Case 9.—J. L., a 13 month old white girl, was admitted to the hospital on the eighth day of paroxysmal cough, with twitchings of the right arm. The temperature was 102 F. The lungs and ears showed no abnormalities. The following day there was sudden onset of convulsions, with gasping respirations and cyanosis. The patient died four hours later.

Necropsy.—Brain: Gross examination: The brain weighed 985 Gm. There were subarachnoid edema and congestion of the meningeal blood vessels.

Microscopic examination: There were edema of the meninges; small subarachnoid and subpial extravasations of blood; slightly increased mononuclear cellularity of the meninges; a few perivascular hemorrhages in the cerebral cortex, in the globus pallidus and in the white matter of the cerebellum; a few lymphocytic plugs in the veins of the cerebellum and of the pons, some of which contained a few strands of fibrin, and eosinophilic degeneration of a few ganglion cells of the thalamus. The Purkinje cells were not remarkably degenerated. (Sections of the hippocampus were not available.) An increased number of mononuclear cells (fibroblasts, phagocytes) was noted in the adventitia of a vein in the thalamus.

Other Organs: The middle ears were normal; the venous sinuses were not thrombotic. Areas of atelectasis, with minimal pneumonia, were noted.

CASE 10.—In H. G. C., a white girl 14 months old, convulsions and twitchings of the mouth developed in the sixth week of pertussis, after a fall from a chair, in which she hit her head. When admitted to the hospital on the same day she had generalized clonic convulsions. The temperature was 102 F. There were a few rales in the chest. The neurologic examination was negative. The spinal fluid was blood tinged. Sedatives were given, and oxygen with carbon dioxide was administered. Later in the day spasticity of the right arm and leg developed, and deviation of the eyeballs to the left was noted; the patient became comatose. The temperature rose to 104.6 F. A diagnosis of a left subcortical vascular lesion was made. The patient died twenty-four hours after the fall.

Necropsy (reported with the permission of Dr. Henry Weinberg, assistant medical examiner).—A horizontal fracture 10 cm. long was observed in the occipital bone. A few minute blood clots were found between the bone and the dura; they were too small to cause bulging of the dura. No gross hemorrhages were seen in the subdural or the subarachnoid spaces.

Brain: Gross examination: The brain weighed 950 Gm. There were congestion of the meningeal veins and diffuse congestion of the brain substance, but no hemorrhages.

Microscopic examination: There were edema of the meninges; rare scattered red blood cells in the subarachnoid space; a few small subpial hemorrhages; a minute perivenal hemorrhage in the wall of the third ventricle; a minute hemorrhage in the cortex of the cerebellum (traumatic?); a minute hemorrhage in the hippocampus; congestion of cerebellar capillaries, with pericapillary glial alinement; plugs of mononuclear cells in small blood vessels of the cerebellum and the striate body; eosinophilic degeneration of the hippocampal pyramidal cells, of Purkinje cells and of cells of the substantia nigra; moderately wide perivascular and pericellular spaces in the cerebral cortex, and marginal perivascular rarefaction (edema?) of the white matter in the external capsule. Pink-staining large cells with eccentric nuclei and granular cytoplasm (phagocytes?) were noted in these areas. Some common phagocytes with refractile granules in the cytoplasm and lymphocytes were seen in the adventitia of an artery in the external capsule. Clumps of calcium-like material occurred in the walls of several blood vessels in the striate body.

Other Organs: The venous sinuses showed no thrombi. The middle ears contained a yellowish mucopurulent material (Pneumococcus type XXIII). Bronchopneumonia was noted microscopically in several small areas of the lungs.

Culture of the brain was negative for H. pertussis.

Virus studies of the brain gave negative results.

Conclusion.—The degenerative cerebral process antedated the fall and probably was responsible for death.

CASE 11.—P. C., a 2 year old white girl, with a history of pertussis of about three weeks' duration, was admitted to the hospital because of convulsions which began during a paroxysm of cough. She had clonic convulsions, twitchings of the face and head, spasticity of all extremities, exaggerated deep reflexes and absence of the abdominal reflexes. There was slight rigidity of the neck. The pupils were dilated and did not react to light. The eyes deviated to the right. The patient was moderately cyanotic. The chest was resonant; a few coarse rhonchi were present. The oral cavity was filled with tenacious mucus, which

had to be removed by suction. Despite the administration of sedatives, the convulsions continued at ten minute intervals. Later cyanosis became marked and oxygen was administered. The patient died two hours and thirty minutes after admission.

Necropsy.—Brain: Gross examination: Subarachnoid edema was marked; the fluid was blood tinged; small, flat subarachnoid effusions of blood were present over both hemispheres; the gray and the white matter were congested; there was no excess of fluid in the ventricles.

Microscopic examination: There were observed subarachnoid edema; subarachnoid extravasations; wide perivascular and pericellular spaces in the cortex; small subependymal hemorrhages in the hippocampus, with recent rarefaction in the white matter; lymphocytic plugs in small veins of the striate body, of the medulla and of the white matter of the cerebellum; ovoid eosinophilic cells in the perivascular spaces of several veins in the thalamus and in the adjoining brain substance (phagocytes?), and eosinophilic degeneration of some pyramidal cells of the hippocampus, the cortex and the dentate nucleus and of a few Purkinje cells; the Purkinje cells stained faintly with cresyl violet.

Other Organs: Acute bronchitis was present. The venous sinuses contained soft postmortem clots. The middle ears were normal.

Culture of the brain was negative for H. pertussis.

Virus studies of the brain gave negative results.

Case 12.—W. A., a 13 month old white boy, had convulsions, fever and abdominal distention on the fourth week of pertussis. On admission he had tonic spasms of the extremities and at times clonic convulsions. The temperature was 107 F. Moderately advanced pneumonia was diagnosed clinically. The spinal fluid showed a slight increase of protein, but no increase in the number of cells. The next day the rales became more numerous, and the temperature fluctuated between 106 and 107 F. The patient died one and one-half days after admission.

Necropsy.—Brain: Gross examination: The brain weighed 930 Gm. Subarachnoid edema was marked; the meningeal veins were engorged, and the fluid in the ventricles was blood tinged.

Microscopic examination: There were marked subarachnoid edema; moderate widening of perivascular and pericellular spaces in the cerebrum and medulla; perivascular hemorrhages in the striate body and in the medulla (some in the floor of the fourth ventricle); lymphocytic plugs in a few small veins of the cortex, of the medulla and of the striate body; eosinophilic degeneration of the pyramidal cells in Sommer's sector of the hippocampus, with "homogenized" appearance (*Aufklärung*) of this area in cresyl violet preparations; increased number of fibroblasts in the adventitia of several veins in the striate body; occasional calcium-like concretions in the walls of several veins in the striate body and in the brain substance bordering on perivascular spaces, and eosinophilic globules and cells with eccentric nuclei in the perivascular spaces and in the adjoining white matter of the external capsule.

Other Organs: The left middle ear contained some greenish pus (Streptococcus haemolyticus and B. pyocyaneus). Several areas of atelectasis, with incipient superimposed pneumonia, were noted.

Case 13.—D. U., a white boy 18 months old, was admitted to the hospital on the seventh day of pertussis with a diagnosis of pneumonia. On admission the patient had severe paroxysms of cough. There was flaccid paralysis of the right arm and leg. The head was turned to the left; the eyes deviated to the left.

The left pupil was dilated; both pupils reacted to light. Nystagmus was present. The temperature was 99 F., the respiratory rate 20 and the pulse rate 100. Rales were present on both sides of the chest. Soon after admission drooling, grinding of the teeth and incessant movements of the left arm and leg were noted. The temperature rose to 107 F. within two and a half hours. The child was restless, but there were no true convulsions. The spinal fluid was clear and contained 2 cells per cubic millimeter. The child died four and a half hours after admission, after a rise of temperature to 108 F.

Necropsy.—Brain: Gross examination: The brain weighed 1,030 Gm. Subarachnoid edema; congestion of the meningeal veins, with nonadherent blood clots in some veins, and edema and congestion of the brain were noted. There were no gross hemorrhages. Colorless fluid was present in the ventricles.

Microscopic examination: There were subarachnoid edema; occasional red cells in the subarachnoid space and a slightly increased number of mononuclear cells in the meninges; lymphocytic plugs in some meningeal veins; moderate widening of perivascular spaces in the cortex, but no significant cellular degeneration in any part of the brain; small perivascular hemorrhages in the cortex; larger hemorrhages in the floor of the fourth ventricle, in the hilus of the inferior olive, in the dentate nucleus and in the striate body; lymphocytic plugs in a vein in the wall of the third ventricle and in small veins of the pons, and an increased number of fibroblasts in the adventitia of several blood vessels in one area of the striate body. Eosinophilic droplets, varying in size, were massed together in the periadventitial white matter of veins in the external capsule. Droplets were present in the perivascular spaces; they had obviously been extruded from the white matter, which showed round, empty spaces. No nuclei were seen in any of the globular masses, small or large. The larger globules were the size of eosinophilic cells observed in cases 10, 11 and 12. One calcium-like concretion was seen in the wall of a blood vessel in the striate body.

Other Organs: Nonadherent blood clots were present in the dural sinuses; the middle ears were normal. Large areas of atelectasis were present in both lungs, with several very small areas of superimposed pneumonia.

Culture of the brain was negative for H. pertussis.

Case 14.—J. C., a 2 year old Negro boy, was admitted to the hospital, presumably on the seventh day of pertussis, in a semicomatose state, with marked dyspnea and tachycardia. The temperature was normal. The eyes were turned upward; the pupils reacted sluggishly to light. There was marked rigidity. A smear of the spinal fluid showed a slightly increased number of cells, with 95 per cent mononuclears. The blood count revealed 125,000 white cells, with 70 per cent lymphocytes. There were rales in both lungs. No Koplik spots were seen. The next day the patient was in deep stupor and had generalized clonic convulsions. The abdominal and cremasteric reflexes and the knee and ankle jerks were absent; there was an unsustained ankle clonus. The Babinski and Kernig signs were not elicited. In addition to rales, bronchial breathing was heard in several areas posteriorly. During the following two days the patient had occasional convulsions. The temperature rose to 104 F. The patient died four days after admission (on the eleventh day [?] of illness).

Necropsy.—Brain: Gross examination: The brain weighed 1,150 Gm. There were marked edema and congestion.

Microscopic examination: Moderate widening of the subarachnoid space and of the perivascular and pericellular spaces (predominantly in the cortex) was observed. Lymphocytic plugs occurred in the veins of the meninges and the medulla and in the capillaries of the cerebral cortex and the white matter of the cerebellum.

Numerous small areas of demyelination were noted in the white matter of the cerebellum, with small blood vessels containing hyaline thrombi within those areas; some areas contained hemolyzed bodies of red cells and some staining red cells, a few scattered lymphocytes and rare glia nuclei. (Rare swollen myelinated fibers were seen in some demyelinated areas.) Cuffing was not observed. Some Purkinje cells showed eosinophilic degeneration. The optic nerves were normal. Sections of the hippocampus were not available.

Other Organs: Nonadherent blood clots were seen in the dural sinuses. Purulent bronchiolitis and minimal pneumonia were present.

Case 15.—B. McN., an 8 month old white girl, was admitted to the hospital after a week of paroxysmal cough. The temperature was 99 F.; the blood count showed 16,500 white cells, 63 per cent of which were lymphocytes. During the next few days the paroxysmal cough continued, the blood count showed 32,000 white cells, with 85 per cent lymphocytes, and the temperature was elevated. On the sixth day after admission diminished resonance and rales were noted in the right side of the chest, and the temperature rose to 105 F. Twitchings developed in the right side of the face and in the left extremities. Later generalized convulsions occurred. The patient died half an hour after the onset of convulsions.

Necropsy.—Brain: Gross examination: The brain weighed 800 Gm. A flat subarachnoid effusion (about 4 cm. in diameter) was present in the left occipital lobe. Two smaller flat hemorrhages (about 1 cm. in diameter) were noted in the right motor region and over the inferior surface of the cerebellar vermis. (The brain showed no compression by the hemorrhages.) The brain was edematous. No hemorrhages were seen in the brain substance.

Microscopic examination: There were subarachnoid edema; flat subarachnoid hemorrhages; widening of the perivascular and pericellular spaces, most pronounced in the cortex; congestion of capillaries and veins throughout the brain, but no hemorrhages, and occasional lymphocytic plugs. Nerve cells showed no eosinophilic degeneration.

Other Organs: Liquid blood and loose clots were present in the dural sinuses The middle ears were normal. There were bronchitis, peribronchitis and minimal incipient pneumonia (microscopic).

Culture of the brain was negative for H. pertussis.

The pathologic changes observed in this series of 15 cases of pertussis with convulsions were as follows:

	No. of Cases
Edema	14
Eosinophilic cellular degeneration	13
Multiple petechiae in the brain	12
Lymphocytic plugs in veins and capillaries	11
Small subarachnoid hemorrhages	7
Flat, medium-sized subarachnoid hemorrhages as the main lesion	1
Localized meningeal reaction to subarachnoid extravasations	5
Meningitis	1
Pericapillary alinement of glia cells	3
Calcium-like concretion	4
"Globules" and phagocytes (?) in perivascular brain tissue	4
Phagocytes and fibroblasts in vascular adventitia	5
Perivascular loss of myelin (within perivascular hemorrhages; hyaline thrombi in small blood vessels in demyelinated area)	1

Edema.—Edema of the meninges was present in all but 1 instance (case 5). Widening of perivascular and pericellular spaces was present in some degree in most cases, but the use of paraffin technic made it difficult to estimate how much of this change was due to edema and how much to the technic. In the white matter the marginal edema was at times so marked as to simulate a narrow, poorly defined zone of demyelination, but the myelin sheaths in these zones were intact.

Eosinophilic (Ischemic) Cellular Degeneration.—This change was found to be almost as constant as edema. It affected most extensively

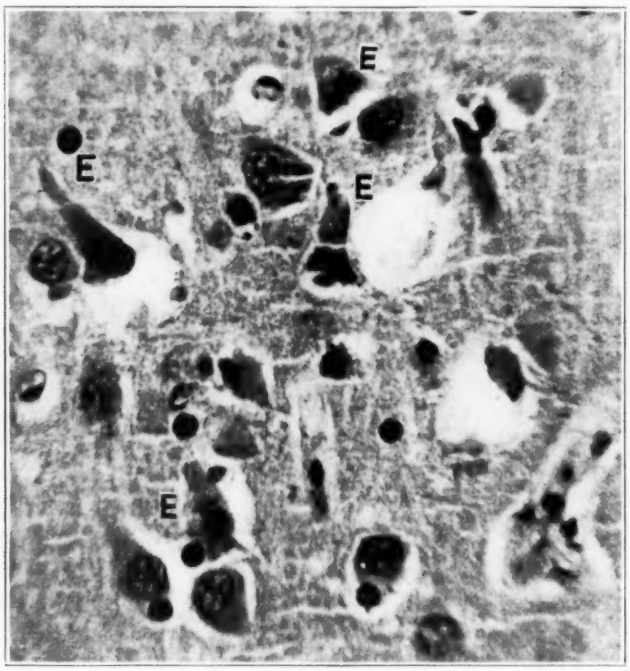

Fig. 1 (case 5).—Eosinophilic (ischemic) degeneration of pyramidal cells of the hippocampus. *E* indicates eosinophilic pyramidal cells with compact pyknotic nuclei. Hematoxylin and eosin; × 500.

the pyramidal cells of the hippocampus (fig. 1) and the Purkinje cells of the cerebellum, but sometimes it affected also the cortex, the basal ganglia, the dentate nucleus and the substantia nigra. In the last-mentioned structure it was readily identifiable because of the absence of melanotic pigment in small children. The Nissl substance of the affected cells lost its ability to stain slightly with the hematoxylin, and the entire cytoplasm of such cells stained brilliantly with eosin. The nucleus of these cells became shrunken and pyknotic. The bright

eosinophilic staining of the cytoplasm might appear before the cells lost their ability to stain with aniline dyes. The cell body might still stain a deep diffuse purple ("sclerotic cells") or a pale diffuse blue with cresyl violet. Only in Purkinje cells the loss of ability to stain with aniline dyes generally coincides with the appearance of diffuse eosinophilic staining of the cytoplasm (homogenizing degeneration of Spielmeyer). The nucleus of the degenerated Purkinje cells becomes shrunken, often stellate and pyknotic, but the cytoplasm in cresyl violet

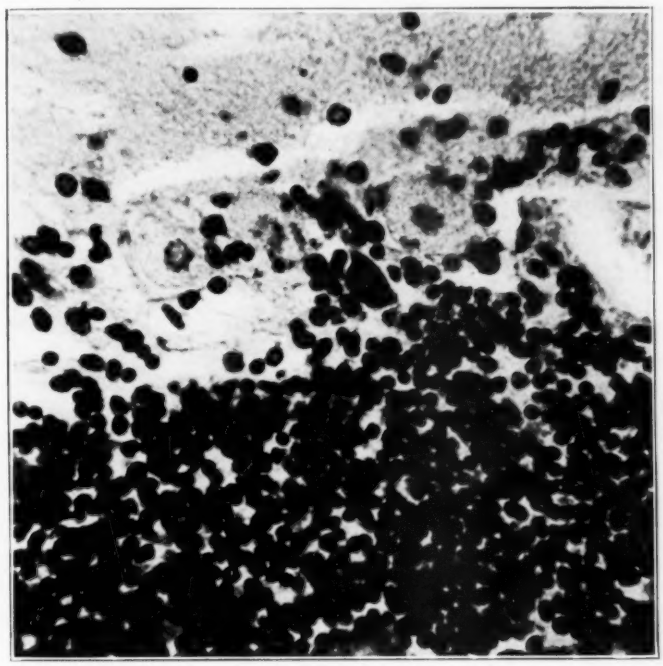

Fig. 2 (case 3).—Homogenizing degeneration of Purkinje cells. Three disk-shaped, barely visible Purkinje cells with shrunken nuclei are present. Cresyl violet; × 500.

preparations is practically colorless, a stage beyond that of "shadow" cells. With the average amount of substage light the homogenized cells may escape notice and appear to be missing; with the substage light cut down to a minimum these cells appear as refractile, slightly opalescent structures, faintly greenish in cresyl violet preparations and often disk shaped, owing to loss of their processes (fig. 2). No glial reaction in the form of *Strauchwerk* was observed around the detached processes of the Purkinje cells.

The number of cells affected by the eosinophilic degeneration in each of the aforementioned areas varied greatly. In the hippocampus either occasional or all pyramidal cells might be affected. If at the same time these cells lost their ability to stain with aniline dyes, the hippocampus appeared rather acellular in cresyl violet stains when examined under low magnification (*Aufklärung* of the German writers); the latter characteristic, appearing at first in Sommer's sector of the hippocampus, was seen but once in this series (case 12, fig. 3).

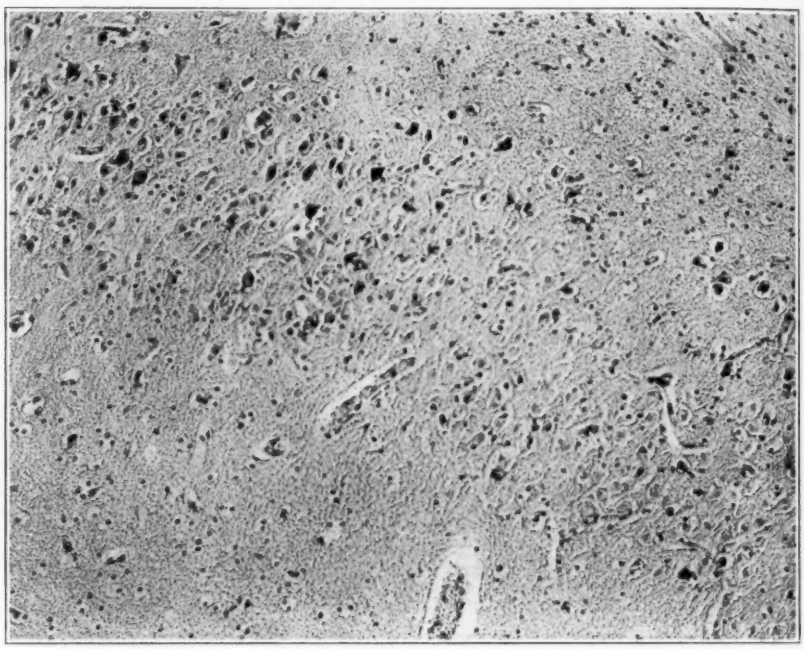

Fig. 3 (case 12).—*Aufklärung* of Sommer's sector of the hippocampus. Loss of Nissl substance in the pyramidal cells of that sector makes the cells barely visible. The cells in the adjoining area take the stain. Cresyl violet; × 49.

In the cerebellum some folia might have numerous homogenized cells, while the neighboring areas showed no such change. King,[20] in his animal experiments with intracerebral injections of extracts of heterologous bone marrow, observed a greater number of homogenized cells on the surface of the cerebellar folia. No such tendency to the distribution of homogenized Purkinje cells has been observed in cases of pertussis.

20. King, L. S.: Encephalopathy Following Injection of Bone Marrow Extract, J. Exper. Med. **70**:303, 1939.

Hemorrhages.—No massive hemorrhages were encountered in this series. Small subpial and subarachnoid hemorrhages were often seen in cases in which other pathologic changes were present. In 1 instance (case 15) several flat subarachnoid hemorrhages, from 1 to 4 mm. in diameter, over the surface of the brain were the major pathologic change in the brain. The hemorrhages were superficial and did not compress the convolutions. They could explain the convulsions, but could not produce sufficient compression of the brain to result in death.

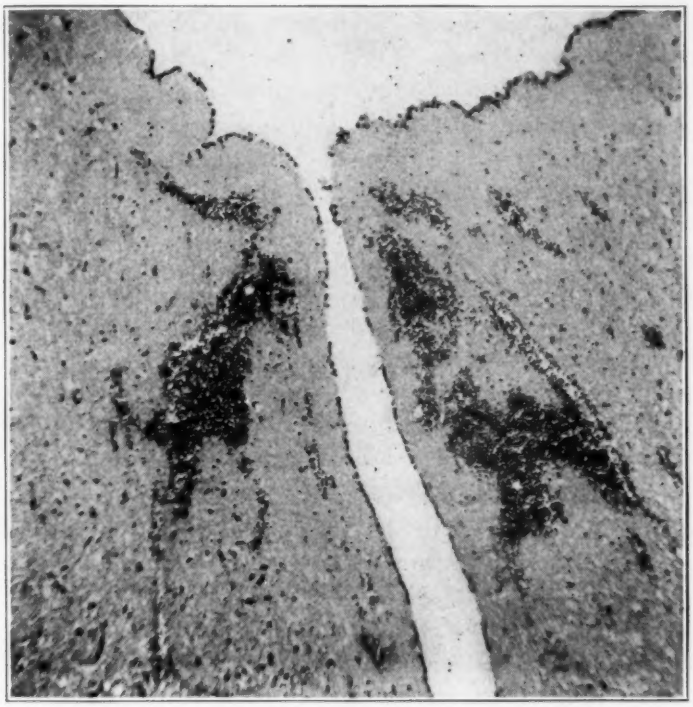

Fig. 4 (case 1).—Hemorrhage in the floor of the fourth ventricle. Hematoxylin and phloxine; × 150.

Death in this case was probably due to some general toxic process, as the patient had a unilateral adrenal hemorrhage and toxic degeneration of the liver.

Multiple petechial hemorrhages, perivascular and infiltrating into the surrounding surface of the brain, were seen in 12 cases, usually in combination with the eosinophilic cellular degeneration. They were most frequent in the white matter, but were seen also in the gray substance. In 5 cases (1, 3, 5, 12 and 13) petechiae were present in the

floor of the fourth ventricle, probably precipitating death (fig. 4). In 1 case (13) multiple small hemorrhages constituted the main lesion observed.

The blood vessels did not show rupture or acute degenerative changes in the areas of hemorrhage or in other parts of the brain.

Lymphocytic Plugs.—Such accumulations, which were seen in 11 cases, usually did not form organized thrombi, but consisted of cellular collections occupying a part of the lumen of a vein or forming a loose column in a capillary, with occasional red cells among the white (figs. 5 *A* and *B*). In a few cases fibrin was present in the mononuclear collections within the veins. Only in case 1 were lymphocytic plugs encountered in organs other than the brain.

Localized Meningeal Reaction.—Although not severe enough to be called meningitis, this reaction was observed in most cases of subarachnoid extravasation. It consisted in a moderate increase in the number of fibroblasts and lymphocytes near the subarachnoid hemorrhages.

Meningitis.—Meningitis was seen in only 1 instance (case 2), which was clinically considered as one of meningococcic meningitis and in which antimeningococcus serum was given intrathecally. The exudate consisted of lymphocytes, macrophages and some polymorphonuclears. It is possible that its original morphologic character was modified by the administration of the horse serum.

Pericapillary Alinement of Glia.—Such a response was observed in 3 cases, in 1 of which it occurred in the white matter of the hippocampus. Stains for fat in the hippocampus in this case and in several other cases did not reveal any accumulation of fat except for minimal, dustlike particles in cells of the microglia type.

Calcium-like Concretions.—These bodies, giving a negative reaction for iron, were seen in the striate body, in the adventitia of blood vessels or in the brain tissue adjacent to perivascular spaces.

Globules.—Such droplets, which stained pink with eosin and the diameter of which varied from that of a red cell to one four times as great, were observed chiefly in the striate body, particularly in the external capsule. Similar structures could be observed free within the perivascular spaces. At times round, empty spaces could be seen in the adjacent brain tissue, suggesting that the droplets were extruded from that tissue into the perivascular space. In 1 instance (case 13) only globules were observed. In other cases, in addition to the droplets, cells with homogeneous or granular pink cytoplasm and eccentric small,

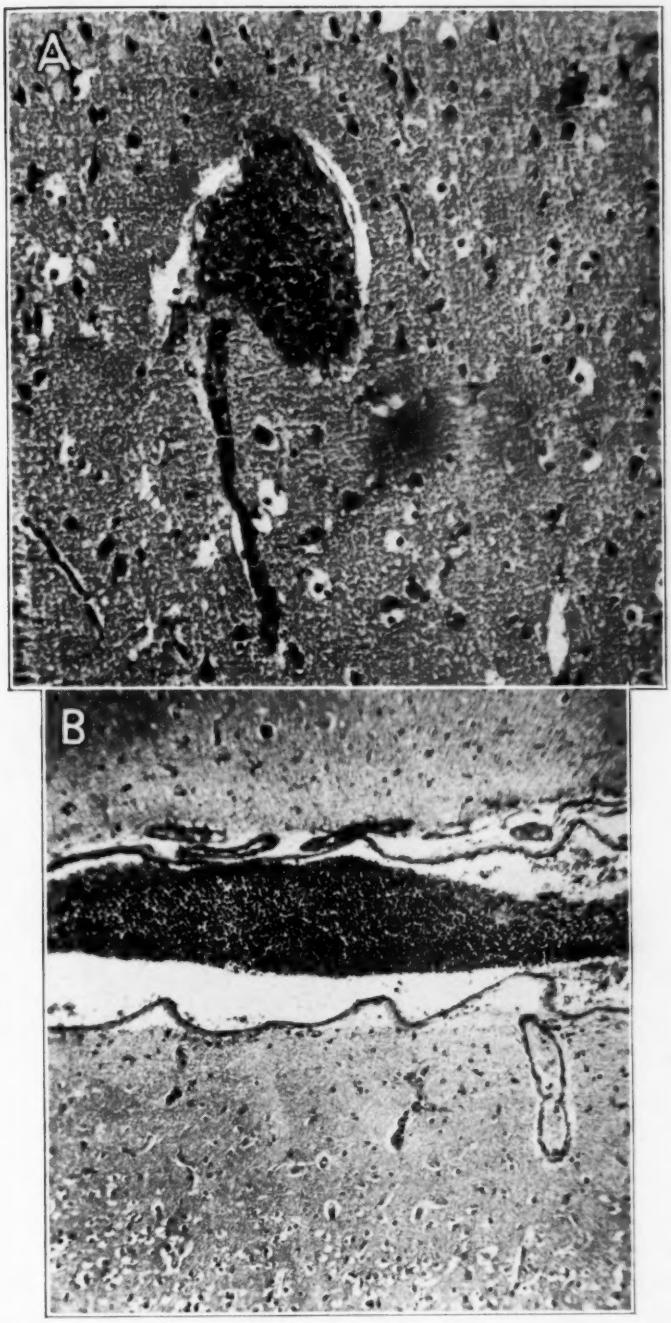

Fig. 5.—*A*, lymphocytic collections in small cortical veins (case 1). Hematoxylin and phloxine; × 390.

B, lymphocytic plug in a meningeal vein (case 14). Hematoxylin and phloxine; × 110.

compact nuclei were seen in the brain tissue and in the perivascular spaces. Some cells had two nuclei (fig. 6). In these cases the globules could be considered sections of cells in which the nucleus was missed. The cells and globules never took the purplish stain of plasma cells, to which they bore a resemblance. These structures usually took the grayish green tinge with the Goldner-Masson stain, similar to the

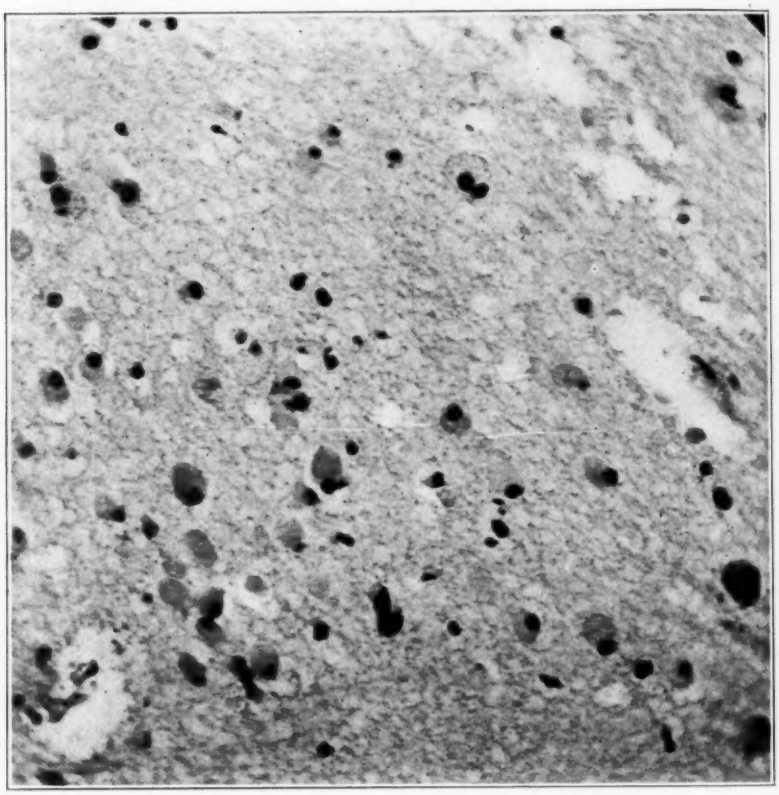

Fig. 6 (case 10).—Phagocytes (?) in the edematous white matter (external capsule). The cells resemble plasma cells in shape but are much larger. The cytoplasm is eosinophilic; the nucleus is compact. One cell near the top of the picture has two nuclei. Hematoxylin and eosin; × 400.

staining of blood plasma. In 1 case only they took the orange G tinge, like that of the red blood cells. In several cases cells of similar character were seen in the adventitia of blood vessels, in addition to lying free in the perivascular spaces. The impression was that these cells were phagocytes.

Phagocytes and Fibroblasts.—Common phagocytes with refractile granules in the cytoplasm and fibroblasts, observed in the adventitia of blood vessels near areas showing the changes described in the preceding paragraph, probably represented a local reaction to that process, similar to the localized meningeal reaction to hemorrhagic extravasations.

Perivascular Demyelination.—This change (fig. 7) was observed in 1 instance only (case 14). The demyelinated areas corresponded to

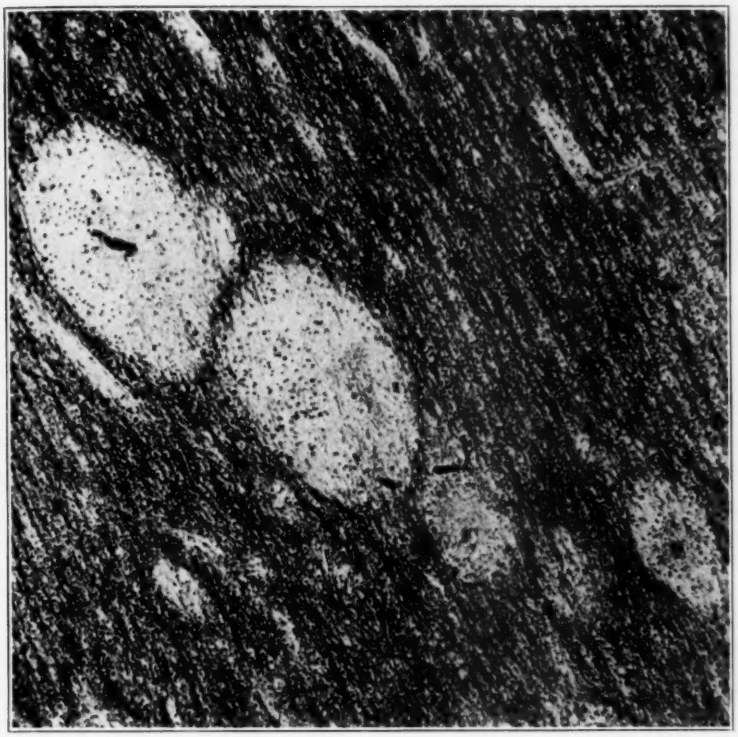

Fig. 7 (case 14).—Perivascular loss of myelin. Hyaline thrombi occur in small blood vessels within the demyelinated areas or at their border. Mahon's myelin stain (King's modification); × 80.

perivascular hemorrhages in which most red cells were hemolyzed, leaving behind poorly staining "shadows" of their bodies. The demyelinated areas usually contained a small vein or a capillary with a "hyaline" thrombus consisting of fused red blood cells (fig. 8). The blood vessel wall showed no degeneration, but sometimes appeared loose, suggesting that the hemorrhages occurred by diapedesis. A few nuclei of lymphocytes, probably escaped with the blood, and rare nuclei of

astrocytes were present in the demyelinated (hemorrhagic) areas. They were more numerous than in the surrounding intact white matter, but were scattered and were never arranged around the blood vessel in the form of a cuff. The impression was that the hemorrhages preceded the degeneration of myelin. Other parts of the brain in this case showed numerous lymphocytic plugs; no loss of myelin was observed in these areas. Eosinophilic Purkinje cells were present in the cerebellum. (No section of the hippocampus was available for study.)

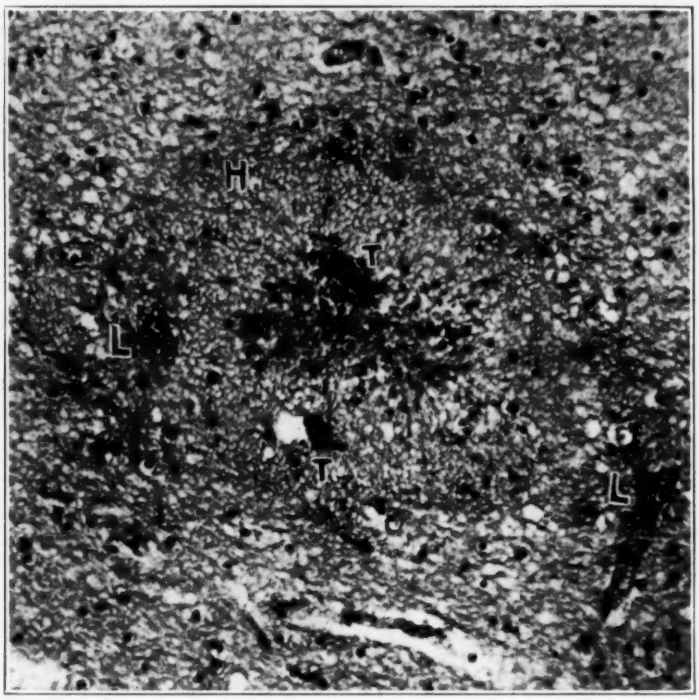

Fig. 8.—Hyaline thrombi and hemolyzed hemorrhage in a demyelinated area. Scattered nuclei of lymphocytes and rare glia nuclei are present within the hemorrhage and at its periphery. *T* indicates hyaline thrombi; *L*, lymphocytic collections in small veins, and *H*, shadows of hemolyzed red cells of the perivascular hemorrhage. Goldner-Masson stain; × 80.

COMMENT

The cerebral complications in pertussis usually manifest themselves clinically as encephalitis. However, as was mentioned before, there is no general agreement in the literature as to whether the cerebral lesions in pertussis should be regarded as histologic lesions of "encephalitis,"

that is, inflammatory lesions produced by an infectious agent (Globus [21]), or be given a designation not implying an infectious inflammatory origin; nor has it been decided whether infection caused by the Bordet-Gengou bacillus (H. pertussis) or by common bacteria plays any role in producing the cerebral lesions. Some of the observations in this series present additional evidence useful in evaluation of the different theories of the origin of these lesions.

Edema of the meninges and brain, the most constant change in this series, does not throw any light on the character of the cerebral lesions, as it may occur in inflammatory, circulatory and degenerative disturbances.

The change next in frequency, the eosinophilic (ischemic, homogenizing) degeneration of the cells of the hippocampus, of the cerebellum and of other areas of the brain, is noninflammatory and is probably not caused by infection. Although this degenerative change is observed occasionally in infectious diseases (Spielmeyer [10]), its occurrence in noninfectious vascular diseases (Neubürger [22]), in epilepsy (Spielmeyer,[23] Scholz [24]), in postanesthesia encephalopathy (Steegmann [25]) and in animal experiments with noninfectious material (King [20]) excludes infection as an indispensable prerequisite for eosinophilic cellular degeneration in the brain. Cerebral circulatory stasis occurring in pertussis (Singer [6]) gives a plausible explanation of the mechanism leading to this essentially anoxemic degeneration.

Venous stasis following functional vasoconstriction also satisfactorily explains multiple hemorrhages. These hemorrhages are sufficiently frequent to be considered an important feature of the pathologic changes in the brain associated with pertussis.

Lymphocytic plugs, which were observed in this series almost as frequently as multiple hemorrhages, have attracted little notice in the literature. Only two papers (Singer [6a] and Fattovich and Lenti [18]) refer to lymphocytic collections in small veins. Singer compared the plugs in pertussis, a disease with high leukocytosis, to plugs of white cells in the leukemias and expressed the belief that they represented early

21. Globus, J. H.: Inflammatory Disease of the Central Nervous System: So-Called Nonsuppurative Encephalitis and Encephalomyelitis, Arch. Neurol. & Psychiat. **28**:810 (Oct.) 1932.

22. Neubürger, K.: Ueber Ammonshornveränderungen bei apoplektischen Hirnblutungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:325, 1927.

23. Spielmeyer, W.: Histopathologie des Nervensystems, Berlin, Julius Springer, 1927.

24. Scholz, W.: Ueber die Entstehung des Hirnbefundes bei der Epilepsie, Ztschr. f. d. ges. Neurol. u. Psychiat. **145**:471, 1933.

25. Steegmann, A. T.: Encephalopathy Following Anesthesia: Histologic Study of Four Cases, Arch. Neurol. & Psychiat. **41**:955 (May) 1939.

stages of thrombosis. Collections of predominantly mononuclear cells in small arteries and veins occur, however, in carbon monoxide poisoning, a condition not connected with a high white cell count (Altschul,[26] Weimann[27]). The latter author accounted for the appearance of these collections by cerebral blood stasis, although he could not find any plausible explanation for the low incidence of polymorphonuclears in the plugs. In this series the mononuclear plugs have been observed in patients whose white blood cell counts in the last days of illness were high (32,000 to 156,000). The lymphocytes always predominated over the polymorphonuclears, as is usual in pertussis. It must be noted that occasionally rare lymphocytic plugs were seen in the brains of patients with pertussis with high white cell counts who had no cerebral manifestations. These plugs must therefore be regarded as a characteristic pathologic feature of pertussis rather than of its cerebral complications. In cases with neurologic manifestations the greater frequency and larger size of the plugs are probably due to stasis. The presence of plugs in the capillaries and veins probably increases the anoxemia in the areas of the brain drained by the plugged vessels. A greater degree of stasis within the brain than in the general circulation may explain the more frequent occurrence of cellular plugs in the cerebral vessels than in other vessels (plugs in the general circulation were observed only once in this series, in case 1).

Toxic action of the endotoxin of the Bordet-Gengou bacillus on the central nervous system has been asserted by some authors to be a possible cause of cerebral complications in pertussis. In animal experiments several workers (Yamaoka,[28] Fonteyne and Dagnelie[29] and others) produced cerebral damage with the endotoxin. However, the lesions were different from those observed in cases of pertussis, and no ischemic cellular degeneration was produced. Although it is known that the Bordet-Gengou bacillus does not invade the blood stream, several brains in this series and some brains in cases of pertussis without cerebral complications were examined bacteriologically for the presence of the bacillus as a possible source of the endotoxin. The material was cultured simultaneously in the laboratories of the Willard Parker Hos-

26. Altschul, R.: Die Einwirkung der Kohlenoxydvergiftung auf das Zentralnervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:442, 1927.

27. Weimann, W.: Zur Kenntnis der Hirnveränderungen bei akuter Kohlenoxydvergiftung, Ztschr. f. d. ges. Neurol. u. Psychiat. **116**:632, 1928.

28. Yamaoka, Y.: Studien über das Keuchhustenbehirn: II. Histopathologische Untersuchungen an mit Keuchhusten-Endotoxin vergifteten Hunden, Ztschr. f. Kinderh. **51**:778, 1931.

29. Fonteyne, P., and Dagnelie, J.: L'action de l'endotoxine coquelucheuse sur les centres nerveux, Compt. rend. Soc. de biol. **110**:978, 1932.

pital and in the Research Laboratories of the New York Department of Health, by Miss Lucy Mishulow. All cultures were negative for the bacillus.

The exotoxin of the Bordet-Gengou bacillus described by Mishulow, Mowry and Scott [30] has, apparently, not yet been used in the experimental study of the cerebral damage associated with pertussis.

In complications of infectious diseases resembling encephalitis the possibility of a superimposed infection with an encephalitis virus is often considered. In 3 cases of this series (1, 10 and 11) material from the brain was inoculated into rabbits and mice by Dr. Margaret Holden, at the department of bacteriology of the College of Physicians and Surgeons (by courtesy of Dr. Josephine B. Neal). The results were negative, so that at least the presence of a virus infectious for those animals was not established.

Some authors consider that pneumonia and otitis media are important predisposing factors in the development of convulsive complications in pertussis. The material in this series does not bear out this contention.

In only 4 of 15 cases were there patchy areas of pneumonia of sufficient size to be of any clinical significance. In 6 others occasional minute, microscopic areas of incipient pneumonia, obviously terminal, arising undoubtedly after the onset of the neurologic manifestations, were observed. In 5 cases the lungs were normal.

Acute otitis media and mastoiditis were present in 1 of the 15 cases. Chronic otitis media, diagnosed clinically, was observed once. Neither the meninges nor the venous sinuses were involved in these cases. Of the remaining cases, mucopus was present in the middle ear and mastoid cells in 1 and a similar material was present in the osseous part of the eustachian tubes in 3. There were no clinical manifestations of otitis media in these cases; the meninges and the venous sinuses were normal. It seems doubtful that inflammation of this character could lead to a fatal cerebral complication. In 4 cases (4, 5, 6 and 11) there was neither otitis media nor pneumonia.

On the basis of the data collected from the literature and of some of the negative evidence presented here, one may say with justification that the lesions in the brain in pertussis are not caused by a local infection of the brain, nor are they caused by a distant action of bacterial toxins from remote infectious foci, as they may occur in the absence of such foci. On the other hand, one may find additional evidence for the circulatory pathogenesis (probably vasomotor stasis) of the lesions observed, as indicated by ischemic (eosinophilic) cellular degeneration and numerous lymphocytic plugs in cerebral blood vessels.

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30. Mishulow, L.; Mowry, I. W., and Scott, E. B.: Pertussis Toxic Fltrates and Toxin-Vaccine, J. Immunol. **19**:227, 1930.

With regard to the term "encephalitis" often used to designate the cerebral lesions in pertussis, one must be aware of the fact that various observers have different criteria as to what constitutes encephalitis from the histologic point of view. Those who consider multiple small hemorrhages in the brain as evidence of hemorrhagic encephalitis would probably classify at least 9 cases of this series as instances of such a condition. Those who regard perivascular and periadventitial cellular infiltrations as necessary for a histologic diagnosis of encephalitis would not place any of the 15 cases in that category.

In several cases in this series some lesions which occur in the encephalitides, but are in themselves not sufficient for the diagnosis of encephalitis, were present. These were (*a*) calcium-like concretions (cases 8, 10, 12 and 13), (*b*) an increased number of fibroblasts and phagocytes in the vascular adventitia (cases 8, 9, 10, 12 and 13) and the presence of eosinophilic "globules" and "phagocytes" in the brain substance bordering on the perivascular spaces (periadventitial tissue) (cases 10, 11, 12 and 13). These changes may be secondary to degenerative processes and could be regarded as an "encephalitic reaction" as understood by Putnam and Alexander.[31] In all but case 13 eosinophilic cellular degeneration was observed; in all but case 8 lymphocytic plugs were present.

In 1 instance in this series, case 14, in which perivascular demyelination was present, the histologic picture closely approximated that of encephalitis occurring in several infectious diseases. However, the perivascular absence of myelin was apparently due neither to primary degeneration of myelin nor to periadventitial cellular infiltration, but to perivascular diapedesis hemorrhages displacing the myelinated nerve fibers and causing secondary degeneration of the myelin sheaths. Hyaline thrombi within the blood vessels in the hemorrhagic areas put this case also in the class of cases with the "encephalitic reaction" of Putnam. This reaction was only a part of the histologic picture in that case, as other areas of the brain showed ischemic cellular changes and lymphocytic plugs characteristic of pertussis.

SUMMARY AND CONCLUSIONS

The changes in the brain in pertussis are apparently noninfectious. They are most likely of circulatory origin and consist in edema, ischemic cellular degeneration, multiple hemorrhages (usually small) and lympho-

31. Putnam, T. J., and Alexander, L.: Disseminated Encephalomyelitis: Histologic Syndrome Associated with Thrombosis of Small Cerebral Vessels, Arch. Neurol. & Psychiat. **41**:1087 (June) 1939.

cytic plugs in veins and capillaries. On rare occasions a secondary "encephalitic reaction" may be observed in addition to the aforementioned changes.

It seems that the term "pertussis encephalopathy," proposed by Jochims, covers most adequately these conceptions and, in the present state of knowledge about the pathogenesis of lesions the brain in pertussis, should be the term of choice for the cerebral complications in that disease.

Dr. Henry Weinberg, assistant medical examiner, gave me permission to report case 10; Miss Lucy Mishulow and Dr. Margaret Holden gave assistance in the bacteriologic and virus studies of several cases, and Mrs. Christine Watson made some of the photographs. Dr. Lewis D. Stevenson gave advice during the preparation of this paper.

OBSERVATIONS ON MONKEYS WITH BILATERAL LESIONS OF THE GLOBUS PALLIDUS

S. W. RANSON, M.D.
AND
CHARLES BERRY, PH.D.
CHICAGO

Wilson [1] made unilateral lesions in the lentiform nucleus of monkeys, which were then kept under observation for about three weeks. Small lesions caused no symptoms. Even when the destruction was extensive tremor or other involuntary movement was not observed. Some of these monkeys, however, showed a preference for using the homolateral limb in grasping food, but there was no real paresis. The symptoms, such as they were, pointed to an impairment of corticospinal fibers, which might be attributed to pressure on, or edema in, the internal capsule associated with the closely adjacent lesion. Wilson's statement "it is therefore conceivable that a large lenticular lesion produces an unsteadying effect in innervation" must be regarded as an impression carried over from his clinical studies rather than a justifiable conclusion drawn from the results of his experiments.

Lewy [2] made bilateral lesions in the lentiform nucleus of monkeys by inserting a knife through a small opening in the skull. These monkeys showed many symptoms of paralysis agitans. There was poverty of movement. When sitting on a rod they showed oscillatory, tottering movements, but never fell. There was cogwheeling in passive motions of the elbow and knee joints. The animals looked old and mummy-like, slept the greater part of the day and usually died of intercurrent pneumonia. No evidence is presented to show that the location of the lesions was checked by subsequent microscopic study. It is difficult to evaluate these results without information as to the extent of damage inflicted on the internal capsule and hypothalamus.

This study was aided by a grant from the Rockefeller Foundation.

From the Institute of Neurology, Northwestern University Medical School.

The Hughlings Jackson Lecture delivered Jan. 29, 1941 at the Montreal Neurological Institute by the senior author presented the essential results of this and some other related investigations, under the title "Some Experimental Studies on the Corpus Striatum."

1. Wilson, S. A. K.: An Experimental Research into the Anatomy and Physiology of the Corpus Striatum, Brain **36**:427, 1914.

2. Lewy, F. H.: Die Lehre von Tonus und der Bewegung, Berlin, Julius Springer, 1923.

METHOD

We wish to report observations made on 3 monkeys with large bilateral lesions in the globus pallidus. The lesions were made by a direct current of 3 milliamperes led in over a nichrome wire electrode, insulated except at the tip. After the current had passed for thirty seconds, the electrode was pushed down 1 mm. and another lesion made. This was repeated two more times. The large lesion in each side of the brain therefore represented four smaller lesions 1 mm. apart along a single puncture, all fused together. The punctures were all made in the frontal plane of the Horsley-Clarke instrument 10 mm. in front of the interaural line. Each of the animals was allowed to live for two weeks and was then killed to permit a study of the brain by the Marchi method.

RESULTS

Lesions.—In monkey 13 the damage was approximately symmetric bilaterally (figure). The following description applies specifically to the damage done on the left side of the brain. The lesion involved the internal medullary lamina and the adjacent parts of the internal and external divisions of the globus pallidus. It left intact the lateral part of the external and the medial part of the internal division of the globus pallidus and the ventral part of both except for the presence of degenerated fibers arising within the damaged area. It involved about one half of the anteroposterior extent of the internal division of the globus pallidus. The rather large part of the external division which extends forward beyond the internal was intact. The internal capsule was slightly damaged where the lesion rested on its lateral surface and where it had been punctured when the electrode was inserted rostral to the plane of the drawing.

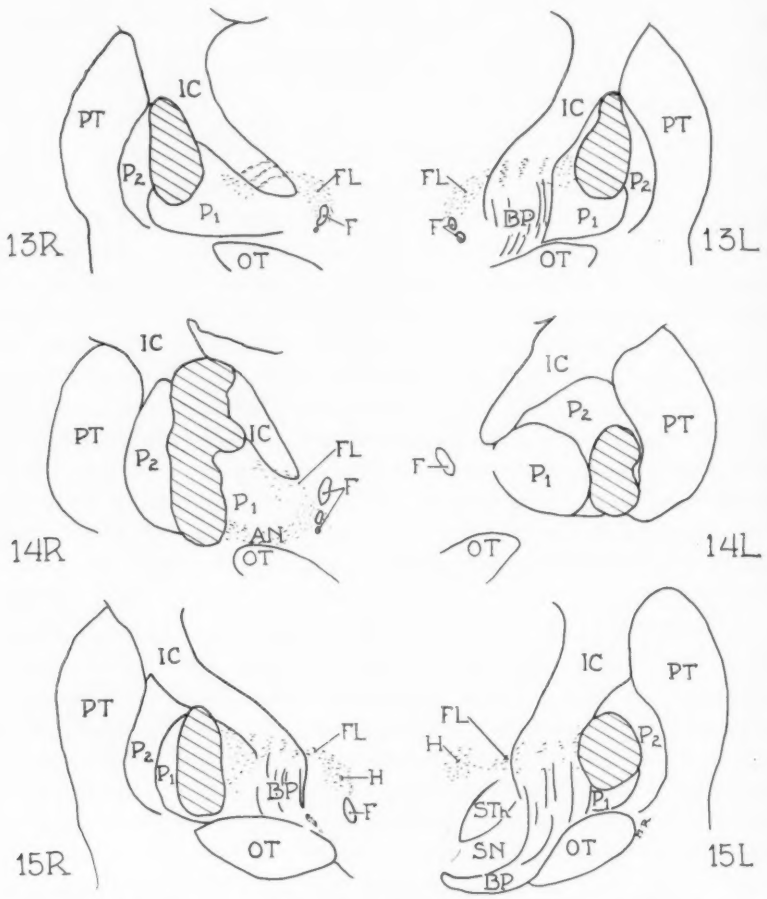
In monkey 14 the electrolytic lesion on the right side was enlarged dorsally by softening due to the interruption of a small blood vessel. It involved the internal medullary lamina throughout its ventrodorsal extent and the adjacent parts of the internal and external divisions of the globus pallidus. The anteroposterior extent of the lesion coincided fairly closely with that of the internal division. The internal capsule was interrupted by the softening, and there was extensive degeneration in the basis pedunculi.

On the left side of the same brain the lesion involved the external division of the globus pallidus, reaching its base but leaving its dorsal part intact. It damaged the ventral part of the internal medullary lamina and injured slightly the ventrolateral border of the internal division. Its anteroposterior extent was about half that of the internal division and less than one-third that of the external division.

In monkey 15 the lesion on the right side was situated in the internal division of the globus pallidus, involving the entire ventrodorsal extent of this nucleus. It damaged the internal capsule. This involvement was

somewhat greater in another plane than that shown in the figure and resulted in a moderate amount of degeneration in the basis pedunculi.

On the left side of this brain the posterior two thirds of the internal division of the globus pallidus was destroyed. The anterior part of this nucleus was intact and the ansa was not degenerated, but the fasciculus



Diagrammatic drawings of frontal sections of the right and left sides of the brain stem of 3 monkeys with lesions in the globus pallidus.

In this figure, *AN* indicates the ansa lenticularis; *BP*, the basis pedunculi; *F*, the fornix; *FL*, the fasciculus lenticularis; *H*, the field H of Forel; *IC*, the internal capsule; *OT*, the optic tract; P_1, the internal division of the globus pallidus; P_2, the external division of the globus pallidus; *PT*, the putamen; *SN*, the substantia nigra, and *STh*, the subthalamic nucleus.

lenticularis was. The lesion involved the lateral border of the internal capsule, and there were some degenerated fibers in the basis pedunculi.

Symptoms.—The monkeys all recovered promptly from the operation. On the first postoperative day one was seen to yawn and another sat with drooping head. But there was nothing approaching the drowsiness seen in monkeys with hypothalamic lesions.[3] There was only slight impairment of motility, such as might be caused by associated damage to the internal capsule. No tremor, athetosis or choreiform movements were noted. During the first week, while the wound was healing, no attempt was made to catch the animals for closer observation. But on the seventh and the fourteenth day monkey 13 was caught and examined, and both the others were caught and examined on the tenth and the fourteenth day.

Monkey 13 was rather active but was easier to catch than a normal monkey. It did not show the poverty of movement and lack of initiative seen in monkeys with hypothalamic lesions. When allowed to run about at the end of a chain the only abnormality noted was a questionable tendency to keep the limbs extended. The grip in the right hand was weaker than that in the left, but the grasp was normal in both feet. The knee jerks were brisk on both sides. On passive flexion and extension no abnormal tonus could be detected in any of the limbs. Neither during the examinations nor at other times when the animal was observed in its cage was there any sign of tremor or of athetoid or choreiform movements.

Monkey 14 was rather easy to catch. The left leg was dragged when the animal walked. This was especially evident when it was allowed to run about at the end of a chain. The left arm and leg were weak, and the grip was weaker in the left hand and foot than in the right. The knee jerk was brisk on both sides. Passive flexion and extension of the limbs disclosed no consistent changes in tonus except for a slight stiffness in the left arm to movement in either direction. At no time during the two weeks that the animal was under observation was tremor or athetoid or choreiform movement observed.

Monkey 15 was active and difficult to catch. It showed a tendency to stand with hyperextended limbs. At times there appeared to be weakness in one limb and at other times in another, but there were no consistent findings indicating paresis. The grip varied from time to time. The knee jerks were brisk on both sides. No increase in resistance to passive movement was detected. Once a very fine tremor was noted in the left arm when this was being flexed against the animal's active resistance. No athetoid or choreiform movements were seen at any time.

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3. Ranson, S. W.: Somnolence Caused by Hypothalamic Lesions in the Monkey, Arch. Neurol. & Psychiat. **41**:1 (Jan.) 1939.

COMMENT

None of these monkeys showed the masklike face, the slowness of movement and the deficient initiative observed in monkeys with hypothalamic lesions which also damaged or destroyed the ansa and the fasciculus lenticularis.[4] Since the masklike face and slowness and poverty of movement were not caused by large pallidal lesions, it seems likely that in the earlier experiments [4] these symptoms were caused by the hypothalamic lesions or by the combined damage to the hypothalamus and destruction of the ansa and fasciculus lenticularis. This raises the question whether damage to the hypothalamus may not play a part in producing the parkinsonian syndrome in man.

SUMMARY

Three monkeys with large bilateral lesions in the globus pallidus showed none of the signs which point to striatal disease in man. None of the animals showed cogwheel resistance to passive movement; none had any trace of a parkinsonian tremor. Choreiform and athetoid movements did not occur. The animals did not have the typical masklike face and slowness of movement characteristic of paralysis agitans.

4. Ranson, S. W., and Ranson, M.: Pallidofugal Fibers in the Monkey, Arch. Neurol. & Psychiat. **42**:1059 (Dec.) 1939.

INTRACRANIAL BLOOD FLOW IN INSULIN COMA

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CINCINNATI

The cause of the coma and other neurologic manifestations which occur during insulin hypoglycemia has been a subject of some controversy among investigators in this field. The most striking and consistent effect of hypoglycemia on the brain is a diminished difference between the oxygen content of blood entering the skull (arterial) and that of blood leaving through the internal jugular veins.[1] Some investigators [2] have attributed this low arteriovenous difference during insulin hypoglycemia to a diminution in the oxygen uptake of the brain, while others have suggested that it may be due to an increased blood flow to the brain.[3] After continuously recording the velocity of blood flow through the internal jugular vein with the Gibbs thermoelectric blood flow recorder [4] in 2 cases, Loman and Myerson concluded that the volume flow of blood through the brain is slightly diminished during insulin hypoglycemia.[5]

From the Departments of Internal Medicine, Neurology and Psychiatry, University of Cincinnati College of Medicine, and the Cincinnati General Hospital.

1. (*a*) Dameshek, W., and Myerson, A.: Insulin Hypoglycemia: Mechanism of Neurologic Symptoms, Arch. Neurol. & Psychiat. **33**:1-18 (Jan.) 1935. (*b*) Himwich, H. E., and Fazekas, J. F.: Effect of Hypoglycemia on Metabolism of Brain, Endocrinology **21**:800-807 (Nov.) 1937. (*c*) Himwich, H. E.; Bowman, K. M.; Wortis, J., and Fazekas, J. F.: Biochemical Changes Occurring in Cerebral Blood During Insulin Treatment of Schizophrenia, J. Nerv. & Ment. Dis. **89**:273-293 (March) 1939.

2. Dameshek and Myerson.[1a] Himwich, Bowman, Wortis and Fazekas.[1c]

3. Abramson, D. I.; Schkloven, N.; Margolis, M. N., and Mirsky, I. A.: Influence of Massive Doses of Insulin on Peripheral Blood Flow in Man, Am. J. Physiol. **128**:124-132 (Dec.) 1939.

4. Gibbs, F. A.: A Thermoelectric Blood Flow Recorder in the Form of a Needle, Proc. Soc. Exper. Biol. & Med. **31**:141-146 (Oct.) 1933.

5. Loman, J., and Myerson, A.: Studies in the Dynamics of the Human Cranio-Vertebral Cavity, Am. J. Psychiat. **92**:791-815 (Jan.) 1936.

On the other hand, Abramson and his co-workers [3] have demonstrated that the volume flow of blood to the muscle and skin of the extremities of man is greatly increased and that the arterial blood pressure also increases. These findings, together with the results of other studies [6] which demonstrated the presence of an increased cardiac output in insulin hypoglycemia, have led these workers to suggest that the blood flow to the brain might likewise be increased.

In order to establish more clearly the cause of the unusually low arteriovenous oxygen difference which characterizes insulin hypoglycemia and thus to gain a better understanding of the cause of the symptoms which accompany it, we have studied the volume flow of blood through the cranium in this condition by a new method which is more direct than those previously available.

METHOD

The method for estimating the volume flow of blood through the intracranial contents of man has been described in detail elsewhere.[7] Briefly, it consists in the measurement of the rate of displacement of cerebrospinal fluid through a large lumbar puncture needle during sudden compression of the neck veins for a few seconds. The principle is similar to that utilized in the plethysmographic measurement of blood flow to the extremities. Compression of the neck veins is effected by sudden inflation of a rubber cuff which surrounds the neck. By using a constant occlusive pressure (60 mm. of mercury) in the cuff and a constant cerebrospinal fluid pressure (200 mm. of water), cerebrospinal fluid displacement rates, repeatedly obtained throughout a given experiment, each bear the same relation to the total intracranial blood flow.

Successful studies were completed on 5 patients with schizophrenia. In each, a series of cerebrospinal fluid displacement rates was obtained over a period of five to fifteen minutes during insulin coma. The subject was then brought out of coma by the intravenous administration of 50 to 100 cc. of a 50 per cent solution of dextrose. Another series of displacement rates was then obtained over a period of five to thirty minutes after the subject had regained consciousness. In 1 of these subjects a series of displacement rates was also obtained before insulin therapy had been instituted.

All determinations were made during periods when the subject was as quiet and relaxed as possible. The blood sugar was determined for

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6. Ernstene, A. C., and Altschule, M. D.: Effect of Insulin Hypoglycemia on Circulation, J. Clin. Investigation **10**:521-528 (Aug.) 1931.

7. (*a*) Ferris, E. B., Jr.: Objective Measurement of Relative Intracranial Blood Flow in Man, with Observations Concerning the Hydrodynamics of the Craniovertebral System, Arch. Neurol. & Psychiat., this issue, p. 377. (*b*) Ferris, E. B., Jr.; Rosenbaum, M.; Roseman, E., and Brower, N.: Objective Measurement of Relative Intracranial Blood Flow in Man, J. Clin. Investigation **19**:773 (Sept.) 1940.

each subject from venous samples obtained just before dextrose was administered. Values below 15 mg. per hundred cubic centimeters were obtained for 5 subjects and a value of 164 mg. for 1 (case 106). Such a high value for blood sugar for the latter appeared related to the occurrence of hypoglycemic convulsions over a period of five minutes preceding the sampling and following the initial series of determinations of blood flow. The subject had regained consciousness before dextrose was administered. During the coma each of the patients sweated profusely.

TABLE 1.—*Cerebral Blood Flow During and After Insulin Coma in Five Patients* *

Date	Case No.	Cerebrospinal Fluid Displacement Rate, Cc. per Minute: During Insulin Coma		Cerebrospinal Fluid Displacement Rate, Cc. per Minute: After Regaining Consciousness	Average Displacement Rate, Cc. per Minute: During Coma	Average Displacement Rate, Cc. per Minute: After Coma
11/21/39	64	133, 126, 100		109, 112, 141, 120	120	121
8/ 5/40	106	126, 114, 109, 114		91, 96, 86	116	91
8/12/40	114	84, 91, 80, 81, 84, 112, 100	Dextrose administered intravenously	96, 102, 89, 96, 73, 68, 98, 100, 109, 92, 94, 84, 96, 89	90	92
9/ 5/40	115	145, 150, 155		160, 160, 145	150	155
10/10/40	117	145, 133, 150, 133		126, 123, 123, 130, 137, 133, 114	140	127
					123	117

* The values represent consecutive determinations made at intervals of approximately two minutes.

TABLE 2.—*Cerebral Blood Flow Before, During and After Insulin Coma in One Patient*

Date	Control Flows	Cerebrospinal Fluid Displacement Rate, Cc. per Minute	Average, Cc. per Minute
10/24/39	Before insulin therapy.....	109, 112, 133, 126, 109, 109, 104	114
11/21/39	During insulin coma.....	133, 126, 100	120
11/21/39	After recovery	109, 112, 141, 120	121

The arterial blood pressure during coma, as compared with that during the period of recovery was moderately elevated in 2 subjects and unchanged in 3.

RESULTS

The results are tabulated in tables 1 and 2. In 3 subjects the average displacement rate of cerebrospinal fluid during coma and that after recovery from coma did not differ significantly. In the remaining 2 subjects the displacement rates during coma appear to be slightly higher than those after recovery. Since the factors which might alter the relation between the cerebrospinal fluid displacement rate and the total intra-

cranial blood flow [7] were carefully controlled throughout these studies, it may be concluded that the total intracranial blood flow during insulin coma is the same as, or slightly higher than, the blood flow soon after consciousness has been regained.

Because the blood flow was followed for only a short period after the return of consciousness, it is possible that the action of dextrose may have influenced the result. Therefore, a series of displacement rates was obtained on a control subject before and after the intravenous administration of 100 cc. of a 50 per cent solution of dextrose. The dextrose had no significant effect on the blood flow. In order to control further the study, a series of displacement rates was obtained on 1 of the treated subjects (case 64) two weeks before insulin therapy was instituted (table 2). The average displacement rates obtained before insulin therapy, during insulin coma and after regaining consciousness were, respectively, 114, 120 and 121 cc. per minute.

CONCLUSIONS

From these studies it may be concluded that hypoglycemic coma, induced by the administration of insulin, is associated with either no change or a slight increase in total intracranial blood flow. The magnitude of the increase which occurred in 2 of the cases is insignificant when compared with the changes in peripheral blood flow and in the oxygen content of jugular venous blood which have been reported.

In view of the consistency of these results, it is apparent that the low arteriovenous differences which occur regularly in this condition cannot be explained on the basis of an increased blood flow to the brain but must be caused by a decrease in the metabolic activity of the brain. It is evident, therefore, that many of the neurologic manifestations of hypoglycemia may be related to cerebral anoxia in spite of the presence of an adequate circulation to the brain.

NOTE.—Since the completion of these studies, Himwich and co-workers [8] have made a preliminary report of a study in which they measured simultaneously the velocity of blood flow through the internal jugular vein and arteriovenous differences before, during and after insulin hypoglycemia. During hypoglycemia the velocity of flow in the jugular vein remained unchanged in some instances and fell slightly in others, findings which indicated to them that changes in the volume flow of blood through the brain during hypoglycemia could not account for the low arteriovenous differences which they found in all subjects.

Nathaniel Brower, Ph.D., gave technical assistance.

8. Himwich, H. E.; Bowman, K. M.; Daly, C.; Fazekas, J. F.; Wortis, J., and Goldfarb, W.: Changes in Cerebral Blood Flow and Arterio-Venous Oxygen Difference During Insulin Hypoglycemia, Proc. Soc. Exper. Biol. & Med. **45**:468-469 (Oct.) 1940.

News and Comment

NEUROPSYCHIATRIC RESEARCH UNIT AT VETERANS ADMINISTRATION FACILITY

Gen. Frank T. Hines, Administrator of Veterans' Affairs, has established a Neuropsychiatric Research Unit at the Veterans Administration Facility, Northport, N. Y. The unit will operate as an integrant part of the Medical and Hospital Service under the direction of Dr. Charles M. Griffith, Medical Director, and under the immediate supervision of Dr. Hugo Mella, Chief, Postgraduate Instruction and Medical Research Division, Medical and Hospital Service, Washington, D. C.

The personnel of the unit includes two senior physicians, namely, Dr. James A. Huddleson, director, and Dr. William J. Turner, who will supervise the laboratory activities under the direction of Dr. Huddleson. In addition, technical assistants, including a biochemist, an assistant statistician, a laboratorian and a laboratory assistant, have been assigned to the unit, as well as a secretary and stenographer.

The functions of the personnel of the unit will be the conduct of clinical and laboratory research in connection with neuropsychiatric disabilities found among veterans. An effort will also be made to standardize diagnostic and therapeutic methods used in connection with the management of neuropsychiatric diseases, and from time to time the personnel of the unit will be engaged in teaching modern concepts of neurology, psychiatry and neuropathology to medical officers of the Veterans' Administration, detailed for this purpose.

NEW YORK PSYCHOANALYTIC SOCIETY AND NEW YORK PSYCHOANALYTIC INSTITUTE

The New York Psychoanalytic Society and the New York Psychoanalytic Institute elected the following officers for 1941-1942: president, Adolph Stern, M.D.; vice president, Lillian D. Powers, M.D.; secretary, Philip R. Lehrman, M.D.; treasurer, Samuel Atkin, M.D.

The following are on the board of directors: Samuel Atkin, M.D. (executive director); Carl Binger, M.D.; Smiley Blanton, M.D.; Leonard Blumgart, M.D.; Isra T. Broadwin, M.D.; Phyllis Greenacre, M.D.; John A. P. Millet, M.D.; Lillian D. Powers, M.D.; Adolph Stern, M.D., and Philip R. Lehrman, M.D.

The following are on the educational committee: Samuel Atkin, M.D.; Leonard Blumgart, M.D. (chairman); Sara Bonnett, M.D.; Lawrence S. Kubie, M.D.; Philip R. Lehrman, M.D.; Sandor Lorand, M.D.; Lillian D. Powers, M.D.; Sandor Rado, M.D.; Adolph Stern, M.D.; J. H. W. van Ophuijsen, M.D., and Fritz Wittels, M.D.

Dr. Leonard Blumgart was elected to the executive council of the American Psychoanalytic Association and Drs. Philip R. Lehrman and Sandor Rado were elected to the council on professional training of the American Psychoanalytic Association.

Obituaries

PROF. DR. HANS BERGER

1873–1941

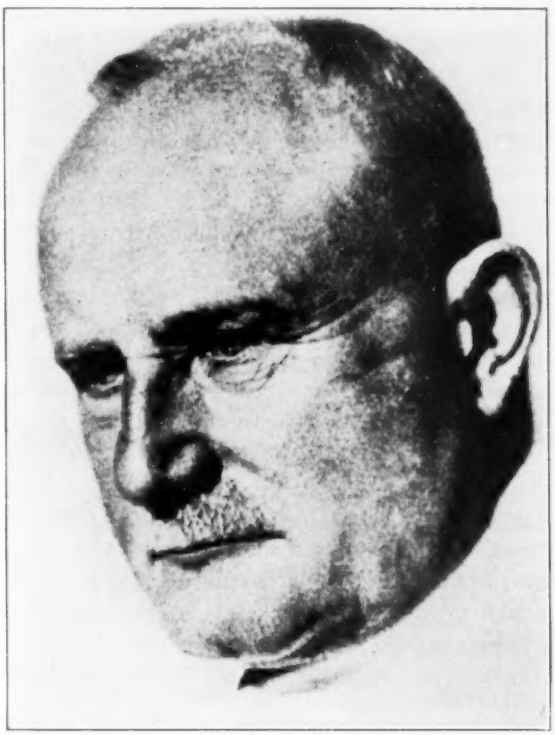
Hans Berger was born May 21, 1873. His great work on the electrical activity of the human cortex was not begun until he was 49 years of age, but the drama of his life had such unity of scene and continuity of action that it all seems an integral part of his masterpiece. From his youth on, he was closely identified with the University of Jena. Most people spoke of him as Hans Berger of Jena, as though that were part of his name. He was appointed privatdozent there in 1901, *ausserordentlicher* professor of psychiatry in 1905, and full professor and director of the University's Clinic for Nervous and Mental Disease in 1919. He died in Jena on June 7, 1941.

From the start of his scientific life he tried to find physical changes in the brain which correlate with mental activity. In his first work, he studied the cerebral circulation in man, using volume changes inside the skull, the form of the cerebral pulse and the interval between the pulse in the brain and that at other points in the body to indicate the condition of the cerebral vascular bed. The results of these investigations were not startling. They are described in detail in two of his books, "Zur Lehre von der Blutzirkulation in der Schädelhöhle der Menschen" (1901) and "Ueber die körperlichen Aeusserrungen psychischer Zustände" (1904). He next turned his attention to the study of the temperature of the brain. With a special thermometer, 1.5 mm. in diameter, inserted into the brain, he read cerebral temperature to an accuracy of 0.01 degree. But again he was disappointed, for he found no good correlations between the temperature of the brain and changes in states of consciousness. He was not unduly discouraged, however, and he did not abandon his organic approach to psychiatry. In 1915 he published "Trauma und Psychose," and in 1927, "Ueber die Lokalisation im Grosshirn."

When he undertook his studies on the electroencephalogram, in 1924, he had at the outset certain great advantages. In the first place, he believed that mental activity might be associated with electrical activity. Most of his informed contemporaries held that this was improbable. He knew that some sort of electrical activity could be recorded from the brain because he had recorded it himself in 1903, and he was aware of the work of Caton, Beck, von Marxow, Gotch and Horsley. He had acquired facility in dealing with rhythmic phenomena in his studies

on the cerebral pulse and realized that slight differences in wave form and changes in duration may have great significance. He had as close neighbors in Jena the Zeiss Optical Works and its technicians to help him with the optical amplification of the very minute phenomena which he encountered.

His discovery that the human brain has an electrical beat and that this beat varies with various mental states was revolutionary. To appreciate how revolutionary, one must remember that in 1929, when



PROF. DR. HANS BERGER
1873-1941

Berger published his first paper on the electroencephalogram, the psychologic schools of psychiatry dominated by freudianism were definitely in the ascendant and the type of psychiatry which seeks a physical basis for psychic processes was more or less in eclipse. It should be remembered also that the neurophysiologists of that time were focusing their attention on the "single unit" and that the concept of masses of nerve cells was taboo. The changes in direction that have occurred in psychiatry and neurophysiology since 1929 cannot all be credited to

Berger, but he was directly and indirectly responsible for more than is generally supposed. It would be inaccurate to relate that this reorientation occurred without the development of tensions, and that these tensions did not reveal the usual flaws in human nature. There were many who ridiculed Berger; there were some who tried to patronize him. His German colleagues were willing to agree that he was a good psychiatrist and that he could speak surprisingly well on occasion, but they were puzzled and amused by his talk about electricity in the brain. He had got beyond his depth, they thought. He was often called jokingly *der treue Hans,* after a famous mathematical horse.

Outwardly, at least, Berger was not disturbed by lack of recognition. He knew that he was right and that his critics were storing up confusion for themselves. He realized that he was being opposed by human inertia rather than by individuals, and that time alone could overcome the lag. He was greatly pleased when in 1937 he was invited to preside as co-chairman with Adrian at the symposium on electrical activity in the nervous system, held by the Congress of Psychology in Paris. When, at that time, Professor Baudouin hailed him as the most distinguished of all the visitors to his laboratory, he was overwhelmed, and tears came to his eyes as he replied, "In Germany I am not so famous." A trip to the United States was planned for him to visit laboratories where electrical studies on the brain were in progress and to give a series of lectures. He was delighted at the prospect and began polishing his English for the occasion. Then the war broke out—he wrote, "I will come when the international situation permits."

Hans Berger was not spectacularly brilliant; he was honest, kind, intelligent, determined, clear-sighted and independent. These sound like common virtues; in him they were attributes of greatness. His towering achievement stands as his monument. It is renewed proof of how much a single very human spirit can accomplish. The technic which he discovered now ranks as one of the chief tools of neurology and psychiatry.

FREDERIC A. GIBBS, M.D.

Abstracts from Current Literature

Anatomy and Embryology

THE TELENCEPHALIC ZONAL SYSTEM OF THE TELEOST CORYDORA PALIATUS. RUTH N. MILLER, J. Comp. Neurol. **72**:149 (Feb.) 1940.

Six brains of the silurid Corydora paliatus were cut in cross or sagittal planes and stained for cells or fibers. A wax plate reconstruction was made of the telencephalon, olfactory bulbs, stalks and crura. The telencephalon, exclusive of the olfactory bulb and stalk, was observed to be completely everted, with a thin membranous pallium surrounding it laterally and dorsally. Within this epithelial lamina were enclosed the rostral poles of the telencephalon proper together with the crura and the caudal end of the stalk. The intraventricular surface of the telencephalon proper was marked laterally and dorsally by a deep fissure, which extended from the rostral pole caudalward to a position rostral to the region of the anterior commissure, where it became flattened, and from there was continued to near the caudal pole by two shallow sulci. Cell columns of the telencephalon ran longitudinally from the rostral to the caudal pole. The main fiber systems in the telencephalon were the medial olfactory tract, the lateral olfactory tract, the medial and lateral forebrain bundles and the anterior commissure.

ADDISON, Philadelphia.

AN ANALYSIS OF THE PROBLEM OF EMERGENT FIBERS IN POSTERIOR SPINAL ROOTS, DEALING WITH THE RATE OF GROWTH AND EXTRANEOUS FIBERS INTO THE ROOTS AFTER GANGLIONECTOMY. W. H. L. WESTBROOK JR. and S. S. TOWER, J. Comp. Neurol. **72**:383 (April) 1940.

Adult cats were used for this study. In each animal three dorsal root ganglia, the seventh cervical to the first thoracic or the eighth cervical to the second thoracic, were removed from one side. Two weeks to a month later, a number of deganglionated dorsal roots were severed immediately at their emergence from the cord and left in situ. After a further period of two weeks, the deganglionated dorsal roots together with the adjacent portion of the spinal cord were removed and studied by silver technic for intact fibers, both in attached and in detached roots, and by the Marchi technic. No evidence was obtained that any nerve fibers, myelinated or unmyelinated, emerged from the central into the peripheral nervous system through the posterior roots.

FRASER, Philadelphia.

MORPHOLOGY OF THE CEREBELLAR NUCLEI IN THE RABBIT AND CAT. R. S. SNIDER, J. Comp. Neurol. **72**:399 (April) 1940.

Serial sections of the cerebellum of 17 adult rabbits and 6 adult cats were available for this study. Some of the series were stained for Nissl bodies, and others were studied by the silver technic. The central cerebellar gray masses were reconstructed by projecting serial sections onto calibrated paper. The nuclei are shown in relation to the principal cerebellar fissures. In the rabbit the nucleus fastigii, the nucleus interpositus and the nucleus dentatus are fused with each other in a continuous series. In the cat the nucleus fastigii is distinct, but the nucleus interpositus and the nucleus dentatus are fused. The nucleus dentatus is the most compact nuclear mass in both animals and is composed predominantly of large cells.

ADDISON, Philadelphia.

CORTICAL LAMINATION IN THE MONOTREMATA. A. A. ABBIE, J. Comp. Neurol. **72**:429 (June) 1940.

Abbie studied coronal sections of the whole brains of Ornithorhynchus and of Tachyglossus. He recognized fourteen cortical modifications in the brains of the two forms. The neopallium in the monotremes comprises two distinct formations, one related to the hippocampus and the other to the piriform lobe. These two formations meet at an abrupt boundary, which emphasizes their differences. Abbie labels these formations parahippocampal and parapiriform, respectively. No "insular" cortex could be identified because of the lack of claustrum. Abbie's observations do not support Brodmann's views as to the primary six layering of the cortex.

FRASER, Philadelphia.

THE HYPOGLOSSAL COMPLEX OF VERTEBRATES. JOHN WALTER BARNARD, J. Comp. Neurol. **72**:489 (June) 1940.

Barnard has studied both cell and fiber preparations of the brains of frog, turtle, lizard, alligator, bird, opossum, shrew, bat, mouse, rat, rabbit, sheep, dog, cat, macaque and man. The hypoglossal nucleus was identified in the frog as a discrete nucleus, with no accessory nuclear groups. Reptiles showed a slightly greater complexity in the organization of the hypoglossal nucleus, but the hypoglossal nucleus of birds showed a great advance over that of reptiles. The outstanding feature was a clear division of the nucleus into a dorsal and a ventral portion. The hypoglossal nucleus in mammals was more completely separated spatially from the spinal cord than in lower forms. Generally about five subdivisions were found in the hypoglossal nucleus of mammals: (1) a medial group, near or on the midline, (2) a ventrolateral column, extending laterally from the medial group, (3) a small, ventrally situated group of cells, which in some instances ran out along the root fibers, (4) a dorsolateral nucleus and (5) a dorsomedial nucleus, which was usually fused with the last-mentioned group. That each of the subdivisions innervated a more or less discrete peripheral unit of muscle was shown experimentally in the dog. The hypoglossal nucleus of vertebrates above tailed amphibians is a portion of the anterior horn column which finds itself functionally more closely related to the brain stem than to the spinal cord. No evidence of proprioceptive fibers from the tongue was found.

FRASER, Philadelphia.

GRAFTING OF LIMBS IN PLACE OF THE EYE IN AMBLYSTOMA. JEAN PIATT, J. Exper. Zool. **86**:77 (Feb.) 1941.

Rudiments of the right forelimb were grafted homoplastically in place of the right eye in embryos of Amblystoma punctatum, stage 29. In one series of 175 embryos the wound was previously cleaned, and in another series of 175 embryos only the eye bulb and the covering ectoderm were removed. In the embryos in which well formed limbs developed the arrangement of the intrinsic musculature of these limbs was completely normal, and the pattern of distribution of the nerves was usually normal, regardless of the nerve source. In no case did an eye muscle nerve enter a limb directly, but in some instances eye muscle nerves anastomosed with others which did enter the limb, that is, aberrant branches from nervus ophthalmicus profundus V and nervus ophthalmicus superficialis VII. In both series eye muscles were present to some degree, in spite of the removal of mesenchyme from the wound at the time of operation. These eye muscles were inserted directly on or adjacent to the base of the transplanted limb. Movement of the limb, when it occurred, was feeble, and the limb moved as a whole in coordination with the contralateral intact eye. It was concluded that the coordinate movements of limb and eye were due to the contraction of eye muscles, rather than to homologous responses of nonhomologous limb muscles resulting from innervation by eye muscle nerves.

WYMAN, Boston.

Physiology and Biochemistry

MODIFYING ACTION OF CERTAIN DRUGS (AMINOPHYLLIN [THEOPHYLLINE WITH ETHYLENE DIAMINE U. S. P.] NITRITES, DIGITALIS) UPON EFFECTS OF INDUCED ANOXEMIA IN PATIENTS WITH CORONARY INSUFFICIENCY. R. L. LEVY, H. G. BRUENN and N. E. WILLIAMS, Am. Heart J. **19**:639 (June) 1940.

Levy and his co-workers studied the effect of various drugs on the occurrence of pain and on the form of the electrocardiograms of 10 patients with coronary sclerosis. The technic used was that for inducing oxygen want by enabling the patient to breathe a mixture containing a constant percentage of oxygen at a rate comparable to that for normal pulmonary ventilation. The data on 86 tests and 739 electrocardiograms were pooled, averaged and compared with data in control experiments. 1. Theophylline with ethylene diamine in doses of 0.48 Gm. intravenously prolonged the appearance of pain in 63 per cent and diminished the RS-T deviation by 58 per cent. The T waves were modified in 7 of the 10 patients. 2. Glyceryl trinitrate caused a prolongation of 51 per cent in the time of appearance of pain and diminished the RS-T deviation by 47 per cent. The T waves of 6 patients were modified. 3. Theophylline with ethylene diamine prolonged the appearance of pain in 26 per cent, diminished the RS-T deviation by 32 per cent and modified the T waves of 4 patients. 4. Lactose caused only a 2 per cent prolongation in the time of appearance of pain, and the change in the RS-T deviation was 13 per cent. The T waves of 4 patients were modified. 5. Erythrityl tetranitrate prolonged the appearance of pain of 2 per cent of the patients, diminished the RS-T deviation by 26 per cent and modified the T waves of 4 patients. 6. Digitalis shortened the time of appearance of pain by 9 per cent, diminished the RS-T deviation by 40 per cent and modified the T waves of 7 patients. There were no constant relation between changes in heart rate, blood pressure, the occurrence of anginal pain and changes in the form of the electrocardiogram. It appears that when theophylline with ethylene diamine is taken orally it exerts a beneficial action in certain cases of cardiac pain by causing dilatation of the coronary vessels. The result probably depends on the anatomic condition and physiologic state of the coronary circulation. Criteria for the selection of suitable cases are not yet at hand. Glyceryl trinitrate dilates the coronary arteries of patients with coronary sclerosis, and for this reason, not because it lowers systemic blood pressure, it is effective in relieving anginal pain. Erythrityl tetranitrate is not effective in raising materially the threshold for cardiac pain. The increase in the tendency to pain produced by digitalis does not appear to be due to coronary constriction.

J. A. M. A.

BERIBERI AND VITAMIN B_1 DEFICIENCY. E. B. VEDDER, Am. J. Trop. Med. **20**:625 (Sept.) 1940.

Vedder discusses the recent nutritional experiments on beriberi. A review of the work on vitamin B_1 suggests the possibility that degeneration of the nerves and the spinal cord may be produced by the deficiency of vitamins other than B_1. Under certain circumstances deprivation of vitamin A is capable of producing degenerative changes in the nervous system in at least puppies, rats and fowls. It may have a similar effect on human beings subsisting on a diet deficient in fat and vitamin A. Synthesization from the vitamin G (B_2) complex of a few of its six or more factors, namely, nicotinic acid, riboflavin and vitamin B_6, and the recognition of pantothenic acid as an unknown hydroxyacid and of beta alanine, has shown that only the last-named factor cures chick dermatitis. The paralysis and the accompanying changes in the peripheral nerves can be prevented by riboflavin. But riboflavin, nicotinic acid or thiamine hydrochloride does not prevent degeneration of the spinal cord. Pantothenic acid was also most effective in eliminating pathologic changes in the spinal cord. The conclusion is that riboflavin is necessary to the growing chick for the normal functioning and maintenance of the nervous system and pantothenic acid for maintaining intact the structures of the spinal cord. From these experiments it is seen that in later years, as experi-

mental diets have become more refined and the nature of the vitamin G (B_2) complex has been better understood, the results have become increasingly definite and specific. Deprivation of certain factors of the vitamin G (B_2) complex can undoubtedly produce demyelination and degeneration of the axis-cylinders of the peripheral nerves and of the spinal cord. There is no such definite experimentation on man. But applying these results to beriberi, it appears that persons living on an exclusive diet of polished rice, as many of the Oriental poor do, are as deficient in vitamin G (B_2) as they are in vitamin B_1 and that the extensive nerve degeneration from which they suffer may well be due chiefly to deficiencies of vitamin A and vitamin G. Those who in addition to the rice eat sufficient fish or meat do not suffer from vitamin G deficiency. When deficiency of vitamin B_1, vitamin A and certain factors of the vitamin G complex exists, profound degeneration of the entire nervous system (a combination of dry and wet beriberi, the mixed disease) is produced, which cannot be promptly cured by thiamine hydrochloride. A complete and adequate diet is the best treatment in these cases after preliminary treatment with thiamine hydrochloride.

J. A. M. A.

THE EFFECT OF THIAMINE DEFICIENCY IN RATS ON THE EXCRETION OF PYRUVIC ACID AND BISULFITE-BINDING SUBSTANCES IN THE URINE. M. E. SHILS, H. G. DAY and E. V. MCCOLLUM, J. Biol. Chem. **139**:145, 1941.

Procedures are given for the determination of bisulfite-binding substances in the urine of rats. A rapid increase in bisulfite-binding substances occurs in the urine of rats on a thiamine-low diet, the rise being proportional to the degree of deficiency and occurring before any other symptoms associated with the deficiency. Administration of thiamine hydrochloride brings the level of bisulfite-binding substances to normal within twenty-four hours. The level of pyruvic acid accounts rather closely for the amount of bisulfite-binding substance or substances. The amount of food intake has a marked influence on the bisulfite-binding substances and the pyruvic acid concentration of the urine. The isocaloric substitution of fat for sucrose in the diet fed to thiamine-deficient rats results in improved growth, but in only partial return to normal in urinary bisulfite-binding substances. In 4 of 5 thiamine-deficient animals the bisulfite-binding substances remained abnormally high until thiamine hydrochloride was given.

PAGE, Indianapolis.

THE INFLUENCE OF THIAMINE DEFICIENCY ON CITRIC ACID EXCRETION. A. H. SMITH and C. E. MEYER, J. Biol. Chem. **139**:227, 1941.

A deficiency of thiamine in the diet results in decreased excretion of citric acid in the urine. However, the results of paired feeding experiments indicate that this decrease is correlated with the diminished intake of food rather than with absence of thiamine per se.

PAGE, Indianapolis.

A STUDY BY MEANS OF THE ELECTRON MICROSCOPE OF THE REACTION BETWEEN TOBACCO MOSAIC VIRUS AND ITS ANTISERUM. THOMAS F. ANDERSON and W. M. STANLEY, J. Biol. Chem. **139**:339, 1941.

Electron micrograms of tobacco mosaic virus deposited on a collodion film show that the molecules are about 280 millimicrons long and 15 millimicrons wide. Micrograms of a mixture of virus and normal rabbit serum show virus particles of normal size and indicate little or no adsorption of particles from normal serum onto the virus molecules. Similar results were obtained with mixtures of tobacco mosaic virus with antiserums to viruses of tomato bushy stunt, potato latent mosaic and tobacco ring spot. A mixture of tobacco mosaic virus and tobacco mosaic virus antiserum from rabbits when dried on a collodion film an hour after mixing and examined by means of the electron microscope shows particles about 60 millimicrons wide and 300 millimicrons long, with fuzzy profiles. The increase in width of the particles and the fuzzy appearance are regarded as indicating that the ends

of asymmetrically shaped molecules from the serum react specifically with the antigen molecules. No reaction between tobacco mosaic virus antiserum and bushy stunt virus was demonstrable. When the mixture of antigen and antiserum is applied to a collodion film several hours after mixing, an irregular framework of thickened antigen molecules may be seen. It is this framework which makes up the antigen-antiserum precipitate. The results demonstrate the usefulness of the electron microscope and of a large and distinctively shaped antigen, such as tobacco mosaic virus, in the study of the antigen-antibody reaction.

PAGE, Indianapolis.

THE CEREBRAL ARC OF THE CORNEAL REFLEX. A. EARL WALKER, J. Nerv. & Ment. Dis. **92**:569 (Nov.) 1940.

Walker reports 4 cases in which cerebral lesions were apparently responsible for reduction or absence of the contralateral corneal reflex. In the first, a tumor originating in the inferior portion of the central convolutions of the left hemisphere, but not increasing intracranial tension, diminished the right corneal reflex. The lesion was confirmed at necropsy, and no disturbance was observed in or around the pons. In the second case, a meningioma over the superior parietal cortex failed to affect the corneal reflex until after successful removal, when the contralateral reflex was greatly reduced. Similarly, in the third case, the right corneal reflex was found to be reduced after exploration and decompression of a cystic tumor beneath the left temporoparietal cortex. In the last case, in which a vascular lesion produced left hemiplegia with hypalgesia, the right corneal reflex was at first absent but later only diminished. To Walker, these observations suggest that at least some of the fibers subserving the corneal reflex reach the cerebral hemisphere and probably the cortex of the contralateral precentral or postcentral gyrus.

MACKAY, Chicago.

A METHOD FOR SHORTENING THE DURATION OF LOWER MOTOR NEURONE PARALYSIS BY CHOLINERGIC FACILITATION. ALEXANDER WOLF, J. Nerv. & Ment. Dis. **92**:614 (Nov.) 1940.

The fact that acetylcholine is released at the neuromuscular end plate suggests that the same "vagus stuff" may act at the synapse between the upper and the lower motor neuron — hence the idea that the cholinergic facilitators might "exercise" a damaged peripheral motor nerve. To test this hypothesis, Wolf severed the sciatic nerve in 17 cats by section or by injection of alcohol. Seven of these animals were given 10 to 20 mg. of acetylbetamethylcholine hydrochloride, 1 to 3 mg. of prostigmine bromide and 100 to 200 mg. of potassium chloride daily in their drinking water, except for frequent omissions for two days a week. The remaining 10 animals received no medication. With equal daily exercise for all 17 cats, the treated animals showed complete recovery from paralysis in seventy-one to one hundred and forty-four days. None of the controls showed any signs of recovery in two hundred days, except those in which recovery was complete in ninety-three days. Trophic ulcers in anesthetic areas were more extensive and healed more slowly in the control animals, and 5 of these died of secondary infection of the ulcers. The same experiment was performed on 24 albino rats—11 of which received medication and 13 served as controls—with similarly striking rapidity of recovery from paralysis in the treated animals. Microscopic studies of the gastrocnemius and sciatic nerves in the rats showed more muscular atrophy, axonal and myelin degeneration and proliferation of endoneural fibers in the control than in the treated animals. Treatment of a series of patients with Bell's palsy with 7.5 to 15 mg. of prostigmine bromide given orally three to six times daily resulted in rapid improvement in most cases of the refractory as well as of the ordinary form of the disease. The earlier medication was started after the onset of palsy, the sooner recovery followed.

Wolf suggests that cholinergic drugs may facilitate the passage of impulses through the lower motor neuron by preservation of acetylcholine bombardment at the dendrites of the anterior horn cells and that neural regeneration is hastened by this constant stimulation. In addition, experimental work by many authors has hinted that the neurohumeral conception may be applicable to other synapses in the central nervous system.

MACKAY, Chicago.

THE METABOLISM OF THE BRAIN. F. C. COURTICE, J. Neurol. & Psychiat. **3**:306 (Oct.) 1940.

By comparing the differences between arterial and venous blood with respect to carbon dioxide with corresponding differences with respect to oxygen in a series of human subjects and in cats, Courtice found that the respiratory quotient of the brain is constant, approaching unity in all cases. This indicates that the brain is utilizing only carbohydrates. Determinations of the blood sugar in specimens taken in correlation with measurement of the arteriovenous carbon dioxide and oxygen differences confirm this result. Such methods give an accurate indication of the metabolism of the brain tissue.

MALAMUD, Ann Arbor, Mich.

THE NEUROHISTOLOGICAL BASIS FOR THE SENSATION OF PAIN PROVOKED FROM DEEP FASCIA, TENDON, AND PERIOSTEUM. GRAHAM WEDDELL and J. A. HARPMAN, J. Neurol. & Psychiat. **3**:319 (Oct.) 1940.

After anesthetizing the overlying tissues, Weddell and Harpman demonstrated that two main varieties of pain can be aroused from deep fascia, peritendinous connective tissue and periosteum: (1) a mild, sharply localized, pricking sensation which disappears as soon as the stimulus is removed and (2) a more severe and diffuse, aching sensation which gradually rises in intensity to a maximum and then slowly recedes to persist for a short time after removal of the stimulus. These sensations are essentially similar to the two main types of cutaneous pain except for some difference in quality and time relation to the stimulus in the second variety. Anatomically, these sensations of pain are subserved by the free nerve terminals borne by finer medullated and nonmedullated nerve fibers, while sensations of pressure are subserved by Vater-Pacini and Golgi-Mazzoni corpuscles in deep fascia. From tendon substance pain can be aroused only near musculotendinous junctions, where it is of the first main variety only and is subserved by an accessory innervation to the neurotendinous endings of Golgi. There is a similar accessory innervation to encapsulated receptors recording touch, pressure and cold sensations. Thus, the varieties of pain are determined by the morphologic disposition at the periphery of the nerve fibers and endings in the various tissues.

MALAMUD, Ann Arbor, Mich.

THE ELECTROENCEPHALOGRAM IN ELECTRICALLY INDUCED CONVULSIONS IN RABBITS. H. LÖWENBACH and R. S. LYMAN, J. Neurol. & Psychiat. **3**:336 (Oct.) 1940.

Löwenbach and Lyman found that the encephalograms obtained during electrically induced convulsions in rabbits did not differ essentially from those obtained during convulsions produced by metrazol. The tonic phase was characterized by a continuous sequence of large spikes having a frequency of 3 to 10 per second, and the clonic phase, by single or double spikes followed by a silent period, the latter indicating cerebral exhaustion and lasting a few seconds, until the normal pattern was gradually resumed. The authors found that at the end of the convulsion muscle action currents may continue into the silent period, and they suggest that the muscular contractions may arise from discharges originating at lower levels of the nervous system. The only difference between convulsions induced electrically and those produced by metrazol consists in the absence of a latent period and the wider range of duration and severity which can be obtained by the former method. This suggests that the electrical method may be preferred to the use of metrazol in therapy, since the undesirable period of anxiety which occurs during the latent phase of treatment with metrazol is thereby removed.

MALAMUD, Ann Arbor, Mich.

SUBCORTICAL (PASSIVE) OPTOKINETIC NYSTAGMUS IN LESIONS OF THE MIDBRAIN AND OF THE VESTIBULAR NUCLEI. N. P. SCALA and E. A. SPIEGEL, Confinia neurol. **3**:53, 1940.

Scala and Spiegel report on a study of the mechanisms underlying subcortical optokinetic nystagmus, or so-called passive nystagmus, in cats and dogs. They find that the anterior corpora quadrigemina must be intact for its production. Unilateral lesions of the anterior quadrigeminal bodies impaired or prevented nystagmus to the opposite side, and only the most rudimentary reactions could be obtained after bilateral lesions. After lesions in the vestibular nuclei, optokinetic impulses may increase the frequency of a spontaneous central nystagmus if synergic in direction; they may diminish its frequency or even reverse its direction if antagonistic. Large lesions of the vestibular nuclei may prevent the appearance of horizontal passive nystagmus in one or both directions. The authors conclude that the vestibular nuclei play an important part in the mechanism of passive optokinetic nystagmus.

DE JONG, Ann Arbor, Mich.

Neuropathology

PINEALOMA. JOSEPH H. GLOBUS, Arch. Path. **31**:533 (May) 1941.

The term "pinealoma" is used to designate any tumor occurring in the pineal region and any neoplasm arising elsewhere in the brain provided the origin can be traced histologically to the pineal body. The term also carries with it certain restrictions and is to be withheld from a tumor in the pineal region if the tumor is histologically not of pineal derivation.

In all 12 cases of pinealoma reported the quadrigeminal plate was the site of origin of the tumor. In some cases the tumor appeared to be partly encapsulated, but in the majority it was invasive. Bilateral symmetric hydrocephalus was found in every case. This is readily explained by the effect of the neoplasm on the underlying aqueduct of Sylvius and the resultant obstruction to the outflow of the cerebrospinal fluid. In all the cases a histologic pattern reduplicating some stage of the normal developing pineal body was established. In some instances a more thorough search was necessary to discover this feature; in others the admixture of ependymal derivatives in a stage of low differentiation made this problem still more difficult. However, the material in general provided sufficient evidence to establish the structural similarity and the common origin of the tumors occurring in the pineal region, in spite of the apparent divergence in their cellular structure. Dissimilar as they appeared, it was possible to match the structure of any one of the tumors with some phase in the histogenesis of the normal pineal body and in this way to trace them to the common source, an embryonal rest of the pineal body.

The clinical manifestations are readily explained by the direct and the indirect influence of the tumor on the brain stem. The direct burden of the tumor is carried by the midbrain and its subdivisions: the quadrigeminal plate, the oculomotor nuclei, the red nucleus, the brachia conjunctiva and the cerebral peduncles, including the pyramidal tracts. The indirect influence is the result of the compression of the aqueduct of Sylvius by the tumor, leading to internal hydrocephalus, which in turn causes some disturbance on the floor of the third ventricle.

Among the clinical features, Argyll Robertson pupils, vegetative disorders (somnolence, polydipsia, polyuria) and ophthalmoplegias, resulting in diplopia, skew deviation and impairment of upward gaze, when added to other evidences of increased intracranial tension, point to an expanding lesion in the region of the midbrain and lead to a fairly secure diagnosis of pinealoma.

WINKELMAN, Philadelphia.

BRAIN DEGENERATION IN YOUNG CHICKS REARED ON AN IRON-TREATED VITAMIN E-DEFICIENT RATION. F. B. ADAMSTONE, Arch. Path. **31**:603 (May) 1941.

In an extensive series of feeding experiments in which young chicks were maintained on a synthetic ration deficient in vitamin E, Pappenheimer and Goettsch

studied a condition of brain degeneration which they designated "nutritional encephalomalacia." The disorder was originally attributed to the lack of vitamin E in the ration, a conclusion which was modified after it was found that wheat germ oil would not entirely prevent the condition. Their latest work, however, and the investigations of other workers lend support to their original view that vitamin E deficiency is an etiologic factor. Experiments which Adamstone has carried out have produced a similar condition of the brain in feeding tests in which vitamin E deficiency is involved, but there are indications that some other factor is also implicated.

As the result of his experiments, the author concludes that nutritional encephalomalacia is caused by at least two conditions occurring simultaneously: (1) a deficiency of vitamin E, and (2) the lack of some heat-labile substance or substances, or the failure or inability of the animal to utilize some substances, if present, under conditions of vitamin E deficiency. WINKELMAN, Philadelphia.

HISTOLOGIC EVIDENCE INDICATIVE OF THE NATURAL OCCURRENCE OF VITAMIN E DEFICIENCY IN THE CHICK. F. B. ADAMSTONE, Arch. Path. **31**:622 (May) 1941.

Adamstone reports that supposedly normal embryos show spontaneous hemorrhage and a histologic picture which is apparently identical with that encountered in vitamin E–deficient embryos. He concludes that vitamin E deficiency can occur in chick embryos under supposedly normal feeding conditions, although in most animals such an occurrence is regarded as rather improbable because of the wide distribution of vitamin E. However, in the chick the developing embryo is dependent on the food materials, including vitamins, stored in the egg by the hen. In times of high egg production it is conceivable that some eggs may lack a sufficient store of certain vitamins if sufficient green food is not available. This being the case, it is to be expected that the embryo would show a reaction to the deficiency even though none was apparent in the adult.

WINKELMAN, Philadelphia.

AMYOTONIA CONGENITA (OPPENHEIM'S DISEASE). LUCILLE R. ANDERSON and DAVID L. REEVES, Bull. Los Angeles Neurol. Soc. **5**:210 (Dec.) 1940.

Anderson and Reeves report the case of a female infant 7 weeks old who had been limp and weak since birth. She was born spontaneously, at full term, and did not cry during the first twenty-four hours. Her weight at birth was 5 pounds 6 ounces (2,438 Gm.). Pneumonia occurred when she was 3 weeks old, after which her condition became worse. No other member of the family had been similarly afflicted. At examination the infant was pale and thin and exhibited inspiratory stridor. Respiration was purely diaphragmatic, and cyanosis appeared when the child cried. The body musculature was atonic; the head fell backward when she was lifted; the arms, though moving normally and without ataxia, were like pieces of rope, and the legs could be placed behind the head. There was secondary anemia; but the blood was cytologically normal, the spinal fluid showed no changes and the reaction to the tuberculin test was negative. The muscles responded feebly to faradic, but not to galvanic, stimuli. Death resulted from bronchopneumonia. Some of the muscle fibers were small and others large. Cross striations were usually scarcely visible, while some of the fibers had undergone hyaline degeneration. Grossly the spinal cord was normal, but microscopic examination showed that the cells of the spinal gray matter, both dorsal and ventral, were few, often without nuclear structure and vacuolated. Hemorrhages were also observed in the cord. The changes were more marked in some areas than in others.

MACKAY, Chicago.

ACUTE SUBDURAL SPINAL ABSCESS. KENNETH H. ABBOTT, Bull. Los Angeles Neurol. Soc. **5**:227 (Dec.) 1940.

Abbott reports the case of a man aged 51 who had received treatment for syphilis for over a year and who noted weakness, paresthesias and unsteadiness in the lower extremities eight days before admission. Examination revealed absence of tendon reflexes in the lower extremities and a positive Babinski response on the right. Ten days later there was complete flaccid paraplegia, with a level of anesthesia at the first lumbar dermatome and loss of sphincter control. The spinal fluid contained 15 cells per cubic millimeter, 54 mg. of sugar per hundred cubic centimeters and slightly increased amounts of globulin. The Wassermann reaction of the spinal fluid was negative. Subsequently, the spinal fluid contained 33 cells per cubic millimeter. Pains continued in the legs and the anesthetic area gradually ascended to the level of the eighth dorsal segment. Death resulted from bronchopneumonia, with signs of meningitis, two months after the onset. Autopsy revealed an accumulation of pus in the spinal subdural space in the lower dorsal and the upper lumbar region, with secondary acute leptomeningitis. There was no infection outside the dura. Abbott states that the symptomatology of subdural spinal infection is similar to that of epidural abscess except for the relative absence of pain in the back. He thinks the presence of only a few cells in the spinal fluid is of importance in the diagnosis.

MACKAY, Chicago.

BILATERAL CORTICAL THROMBOSES. DWIGHT M. PALMER, J. Nerv. & Ment. Dis. **92**:429 (Oct.) 1940.

Palmer reports the case of a right-handed man aged 62 who experienced two cerebral vascular accidents. In the first he suddenly became confused while eating, could not read or find bread on the table and later left the hotel without checking out and became lost for a while. Though able to work as a salesman, he was euphoric but irritable, talkative and unreserved. Eighteen days later he suddenly manifested jargon aphasia, with complete cortical deafness, and understood nothing of what he seemed to read. There was also some apraxia. Six hours later flaccid hemiplegia appeared on the right. Death followed several days afterward. Autopsy revealed an area of softening in each cerebral hemisphere. The older lesion, corresponding to the initial clinical disturbance, was in the superior part of the right temporal lobe and extended into the anteroinferior part of the parietal lobe. Brodmann's areas 41, 42 and 22 and parts of areas 21, 37 and 39 were involved. The other area of softening, corresponding to the final clinical events, was located in the left superior temporal gyrus and extended to include the long gyrus of the insula and the anterior and posterior transverse temporal gyri, embracing Brodmann's areas 41, 42 and 22 and possibly part of areas 21 and 39. In Palmer's opinion, the first lesion in the recessive temporal lobe destroyed associative connections and reduced the number of ways in which the patient could respond to auditory stimuli. The euphoria might have been a camouflage for these deficiencies or a result of the removal of inhibitory pathways. The second lesion, in the dominant temporal lobe, produced the jargon aphasia. The neural processes responsible for the words of this jargon could not have originated in the destroyed parts of the right auditory association area, but must have come from other sensorimotor areas. The psychotic behavior resulted from the bilateral destruction of sensory projections and associative patterns.

MACKAY, Chicago.

DEGENERATION OF THE BASAL GANGLIA ASSOCIATED WITH OLIVOPONTOCEREBELLAR ATROPHY. CHARLES D. ARING, J. Nerv. & Ment. Dis. **92**:448 (Oct.) 1940.

Aring reports the case of a Negro who at the age of 20 began to have spontaneous shaking of the upper extremities; this increased in severity until his death, at the age of 42. Speech was slow, high pitched, monotonous and dysarthric.

Eight months before his death he began to lose weight and strength; somnolence and apathy followed. A younger brother had died at the age of 22 with similar neurologic disturbances, and a younger sister had died at 18 with tremors of the upper extremities, weakness and ataxia of the legs, slurred speech and convulsive seizures. Examination of the patient revealed advanced cachexia, arterial hypertension and sclerosis and pulmonary tuberculosis. There were apathy, disorientation and childishness. The optic disks were slightly pale. There was marked arcus senilis but no Kayser-Fleischer ring. The pupils were unequal, irregular and unresponsive to light. There was no nystagmus. The muscles were wasted and rigid, without a cogwheel phenomenon; the face was staring and expressionless, and elbows were flexed. Rhythmic "wing-beating" movements were present in all extremities and consisted of flexion and extension or abduction and adduction at the rate of 140 per minute. The movements were absent during sleep and were exaggerated by voluntary activity. There were no sensory disturbances; the tendon reflexes were sluggish; the abdominal reflexes were present, and the plantar responses were of flexor type. The spinal fluid was normal. Tests of hepatic function gave normal results. Death was due to miliary tuberculosis, the clinical diagnosis being progressive lenticular degeneration.

At autopsy the entire brain was small, weighing only 860 Gm. The cerebellum and pons were especially reduced in size, and the frontal lobes were atrophic. There was cystic degeneration of the caudate nucleus, putamen, thalamus, brain stem and medulla. Microscopically, the ganglion cells of the cerebral cortex were severely altered. There was no reaction about the cystic cavities in the basal ganglia and the brain stem, but marked degenerative changes in the remaining ganglion cells with neuronphagia and perivascular collections of fat granule cells were noted. The Purkinje cells had almost all disappeared, leaving empty baskets and proliferation of the Bergmann glia, while the granular layer was depleted of many cells. Astrocytic gliosis had occurred in and around the dentate nucleus. The olives were densely gliotic and contained only a few ganglion cells. Advanced demyelination was noted in the brachium pontis, but little in the other cerebellar peduncles. The myelin had also degenerated in the dorsal columns and in the spinocerebellar tracts. The liver was normal. Aring considers the condition closely allied to both progressive lenticular degeneration and olivopontocerebellar atrophy, although differing both clinically and pathologically from each.

MACKAY, Chicago.

SEMINOMA IN AN ABDOMINAL TESTIS WITH A GLIOMA OF THE BRAIN. M. J. BENNETT-JONES and C. V. HARRISON, Brit. J. Surg. **45**:357 (Jan.) 1941.

The authors report the rare coincidence of seminoma of an undescended testicle and a well differentiated astrocytoma of the right frontal lobe occurring in a man of 55. Such a rare association suggests the possibility of an embryonic origin of tumor in two entirely unrelated organs.

STUCK, Denver.

NEUROPTIC ENCEPHALOMYELITIS. V. DIMITRI and J. P. KAEFER, Rev. neurol. de Buenos Aires **5**:318 (Oct.-Dec.) 1940.

Dimitri and Kaefer report the case of a previously healthy man of 35 in whom there gradually developed paresthesia of the legs and diminution of vision, then blindness in both eyes and, finally, complete paraplegia, with a sensory level at the costal margin, within twelve days of the onset. The spinal fluid showed no alteration in the cell count, the protein content or the colloidal gold curve. He died of septicemia fifteen days later.

At autopsy many disseminated lesions were seen scattered throughout the cord, the brain and the optic nerves. The cord from the eighth to the eleventh dorsal segment was necrotic. There was also a small softening in the right parieto-occipital region of the brain. The lesions involved indiscriminately the gray and the white matter of the cord, but spared the cortex and basal ganglia. In the

white matter both myelin and axis-cylinders were usually destroyed, and in places there was slight proliferation of astrocytes and oligocytes. The authors could trace no definite relation between the foci and the blood supply, but the vessels in the lesion appeared congested.

The authors consider that neuromyelitis constitutes a distinct disease, although it is difficult to differentiate its symptoms and pathology from those of other diseases, such as multiple sclerosis and encephalomyelitis. They believe that the condition is due to a filtrable virus, despite the absence of evidences of infection in their case.

PUTNAM, New York.

CLINICOPATHOLOGIC STUDY OF GANGLIOCYTOMA DYSPLASTICUM OF THE CEREBELLUM. U. MAISS, Ztschr. f. d. ges. Neurol. u. Psychiat. **169**:170 (March) 1940.

Maiss reports the case of a 31 year old man who began to complain early in 1938 of occipital pain, especially on lying down and extending his head. Just before Christmas 1938 he vomited on arising one morning, complained of severe headache and had a tonic seizure. He had a few more tonic seizures up to the time of his admission to the hospital, on March 3, 1939. Between attacks he complained of pain in the back of the head, nausea, occasional attacks of headache and dizziness with physical effort. On admission the significant findings were bilateral papilledema and a tendency to fall to the right with the eyes closed. A ventriculogram showed marked dilatation of the lateral and third ventricles. The fourth ventricle was not visualized. Enlargement of the left hemisphere was observed at operation. The patient died on March 15, 1939.

Autopsy showed diffuse enlargement of the left cerebellar hemisphere. The medulla was pushed to the right. The molecular layer of the left cerebellar hemisphere was widened and showed many myelinated nerve fibers. In some parts of the hemisphere this layer contained many myelinated fibers but was not widened. In the areas with widened molecular layers many neuroblasts and mature ganglion cells were seen. Endofibrils were demonstrable in these cells with the Bielschowsky stain. There were no mitotic figures or binucleate cells. Purkinje cells were not seen in the area of the tumor.

The first case of gangliocytoma dysplasticum was reported by Lhermitte and Duclos in 1920. Most of the patients were middle aged (4 being in the fourth decade, 2 in the third and 1 43 years old). Neither sex is particularly susceptible. It is impossible to differentiate this tumor from other cerebellar tumors on clinical grounds alone. Only 1 of the 7 reported patients recovered (Christensen, E.: *Virchows Arch. f. path. Anat.* **300**:567, 1937), being alive one and one-half years after the operation.

SAVITSKY, New York.

Meninges and Blood Vessels

CEREBROSPINAL MENINGITIS. N. MUTCH, Guy's Hosp. Gaz. **54**:282 (Oct. 5) 1940.

The only effective prophylaxis against cerebrospinal meningitis, according to Mutch, consists in free ventilation and the avoidance of overcrowding. Since the survival time of the isolated meningococcus is short, the disease can be contracted only by close association with some one already infected. It was found that the carrier rate of infection could be reduced in dormitories to 5 per cent by spacing beds 3 feet (91 cm.) apart, as compared with a 20 per cent rate with 1 foot (30 cm.) bed interspacing and a 29 per cent rate with a 9 inch (22 cm.) bed interspacing. In the treatment of cerebrospinal meningitis, lumbar puncture and antimeningococcus serum have been replaced by sulfanilamide and sulfapyridine (2-[paraaminobenzenesulfonamido]pyridine) with marked results. Here the superiority of one drug over the other has not yet been determined. In 5,306 cases reported during the war years of 1914 to 1918 mortality was as high as 65 per cent; in 5,093 cases reported for the first six months of 1940 the death rate was only 20 per cent. Lumbar puncture is performed only at weekly intervals or

when definite signs of increased intracranial pressure are observed. The dose, administered in approximately equal quantities for the two drugs, ranged from 3 Gm. for infants to 9 Gm. for adults (down to 15 years), and was given daily for a week in six doses spaced four hours apart in order to maintain a uniform concentration in the body tissues, but allowance was made for adjustments in severe attacks with supplementary intravenous injections of sulfapyridine sodium. Comatose patients were given the drug in powdered form in suspension through a stomach tube. Intramuscular injections were found impracticable for a number of reasons. In view of the frequent occurrence of adrenal hemorrhage in cases of septicemia rapidly terminating fatally, vitamin C, citrus fruits and adrenal cortex extract are tentatively suggested as means of saving life. Since rapid dehydration occurs in unconscious pyrexial patients, a copious fluid intake is recommended either by stomach or by rectal tube or by an intravenous drip of dextrose-saline solution. The author discusses the nature of the infective organism, its path of invasion, the spread of the infection, the clinical varieties of the disease and complications, such as the common occurrence of arthritis. A preparation that is inexpensive, soluble and susceptible of being administered rectally to unconscious patients or to those with troublesome cerebral vomiting is a desideratum.

J. A. M. A.

Treatment, Neurosurgery

ROENTGEN RAY THERAPY IN THE TREATMENT OF HERPES ZOSTER. P. MCCOMBS, A. TUGGLE and C. M. GUION, Am. J. M. Sc. **200**:803 (Dec.) 1940.

McCombs, Tuggle and Guion report the results of treatment of 123 patients with herpes zoster. Seventy-two received roentgen therapy; 51 did not. Forty-eight (39 per cent) were males and 75 (61 per cent) females. In Kechline's series 90 per cent of the patients were males. In this series 4 (3 per cent) were under 20 years of age, 43 (35 per cent) were between 20 and 50, and 76 (62 per cent) were over 50. The highest incidence was in September and October. Five or six treatments of 200 r each, given daily or every other day, were administered. Two hundred kilovolts filtered through 1 mm. of copper and 1 mm. of aluminum at a distance of 50 cm. with a 6 by 15 cm. portal directly over the spinal root ganglia of the nerves involved was employed. The results of therapy indicate the importance of treating patients with herpes zoster promptly, inasmuch as the proportion of cures in the first seven days was 89 per cent, as compared with only 50 per cent after fourteen days. The authors conclude from the study of 72 cases of herpes zoster that roentgen radiation is an ideal agent for relief of the herpetic syndrome and that better results will be had if adequate treatment is started early.

MICHAELS, Boston.

THE USE OF SYNTROPAN IN PARKINSONISM. N. S. SCHLEZINGER and B. J. ALPERS, Am. J. M. Sc. **201**:374 (March) 1941.

Schlezinger and Alpers treated a group of 16 patients suffering from parkinsonism with syntropan (3-diethylamino-2, 2-dimethylpropyl ester of tropic acid) for a period of from ten days to eight months. In no instance was syntropan beneficial in relieving the symptoms until the dose reached 1,200 mg. daily. In 5 cases no improvement resulted; in 2 of these cases satisfactory cooperation was not obtained because of a prolonged relapse. In 11 patients varying degrees of improvement were observed. Excessive salivation was effectively controlled in all cases. Diminution of rigidity and of tremor was noted with doses approximating 1,200 mg. daily, and maximum benefit was obtained with doses of about 2,400 mg. daily. Blurred vision, flushed face and dryness of the mouth did not occur with syntropan therapy until a dose of 3,200 mg. was reached, when mild blurring of vision was noted in 2 cases. The maximum daily dose of syntropan in the treatment of parkinsonism was considered to be 2,400 mg. The authors conclude that syntropan is useful in many cases in which atropine cannot be administered because of the frequently associated toxic symptoms.

MICHAELS, Boston.

METRAZOL AS AN ADJUNCT TO THE TREATMENT OF MENTAL DISORDERS. C. O. CHENEY, D. M. HAMILTON and W. L. HEAVER, Psychiatric Quart. **15**:205 (April) 1941.

The authors report the results of metrazol therapy in 112 cases. A follow-up study of three months or more was made in 104 cases. Considerable attention was paid to the psychologic preparation of the patient prior to the institution of treatment. Hyperextension of the back was employed to prevent spinal fractures. Forty-eight of 51 patients with manic-depressive psychoses improved with treatment and 29 are at home. Fifteen of 16 patients with involutional psychoses improved and 13 are at home. Of 8 psychoneurotic patients, all improved and 7 are at home. Eighteen of 28 schizophrenic patients improved, 7 of whom returnel home.

At the end of three months or more, 57 of 104 treated patients had returned home, 43 having recovered and 14 being much improved. Only 15 failed to benefit from treatment. There were no deaths, no evidence of permanent cerebral damage and no evidence of possible deleterious results. Two cases of compression of the spine are reported. Old fractures were found in 6 cases in which roentgenograms were taken before treatment. It was found in some cases that repeated courses of treatment produced improvement when a single course had been unsuccessful. The writers state: "In patients who have a capacity for recovery metrazol treatment brings about a change which facilitates other forms of treatment and accelerates recovery so that hospital residence is shortened, sometimes in a strikingly dramatic manner. Its judicious use for this purpose is advocated."

SIMON, Worcester, Mass.

THE TREATMENT OF AGITATED AND DEPRESSED MENTAL STATES WITH BENZEDRINE SULFATE AND SODIUM AMYTAL. R. A. CHITTICK and A. MYERSON, Psychiatric Quart. **15**:362 (April) 1941.

The combination of amphetamine sulfate and a barbiturate was suggested by Myerson on the assumption that by proper balance undesirable effects of one drug could be minimized by the other without denaturing too much the beneficial effect of either. Twenty-one patients were treated. One recovered, and 4 were greatly improved, all of whom had a manic-depressive psychosis. Nine patients who had either a manic-depressive psychosis or involutional melancholia showed slight improvement and were more comfortable and more active in the hospital program during and after treatment. Results were progressive during the first two weeks of treatment, and no changes occurred after this period. Three patients with schizophrenia, 2 with manic-depressive psychosis and 2 with involutional melancholia showed no change.

SIMON, Worcester, Mass.

TREATMENT OF CHRONIC SCHIZOPHRENIA WITH INSULIN AND METRAZOL. A. TEIXEIRA LIMA, D. M. UCHOA and E. F. TANCREDI, Arq. Serv. assist. psicopat. estad. São Paulo **5**:121 (March-June) 1940.

Forty-six patients with chronic schizophrenia were treated. Only 3 (6.52 per cent) recovered, all of whom had paranoid schizophrenia. One had been ill almost a year and the other 2 fifteen months. All these patients received insulin. One had to be given another course of insulin a year later.

Social remission signifies that some type of social adjustment is possible, although certain defects persist. Such a result was obtained in 5 cases, in 3 with metrazol and in 2 with insulin. The duration of illness was one and a half, two, three, four and six years, respectively. Two of the patients had catatonia, 2 paranoid schizophrenia and 1 simple schizophrenia.

Mild improvement not sufficient to make social adjustment possible was obtained in 8 cases (17.39 per cent). Six patients received metrazol and 2 insulin. One patient had simple schizophrenia, 3 catatonia, 2 paranoia, 1 hebephrenia and 1 hebophrenic paranoia. Except in the case of 1 hebephrenic patient who was ill

one and a half years, the duration of the disease varied from three to eight months. Two patients became worse, 1 after metrazol therapy and the other after the use of the alternating method of Kuppers, in which metrazol is employed on the day insulin is not. The condition of 28 patients (60.88 per cent) remained unchanged. The best results were obtained in patients with the paranoid form with insulin therapy.

SAVITSKY, New York.

Muscular System

NUTRITIONAL MUSCLE DYSTROPHY AND SEX HORMONES [ANDROGEN AND ESTROGEN]. S. MORGULIS and C. E. RICHARDS, Endocrinology **27**:522 (Sept.) 1940.

Various investigators have postulated an intimate relation between diseases affecting the muscular system and the condition of the endocrine glands. A number of clinical observations have pointed to an association of progressive muscular dystrophy with disturbance of carbohydrate metabolism. It has been demonstrated that the gonads, both testis and ovary, undergo a progressive and marked degeneration during the course of development of nutritional muscular dystrophy.

In order to determine whether substitution of estrogen or androgen or gonadal stimulation might affect the course of muscular dystrophy of nutritional origin, experiments were made on two series of rabbits with experimentally produced muscular dystrophy. In one series of 40 animals, 30 were given intramuscular injections of testosterone propionate, while the remaining 10 animals served as controls. In a second series of 15 rabbits, 10 were given injections at regular intervals of an extract of the anterior lobe of the pituitary containing the gonadotropic factor prepared by the method of Collip; the remaining 5 animals served as controls.

All the animals receiving testosterone showed extensive development of the external genitalia, whereas in the controls these organs showed little growth. However, in all the rabbits treated with testosterone muscular dystrophy developed in the same manner as in the controls. In the animals receiving the injections of the anterior pituitary extract containing the gonadotropic factor, dystrophy developed to the same extent as it did in the untreated control animals. It appears, therefore, that the gonadal atrophy should be regarded only as a by-product of a general metabolic disturbance which results in muscular dystrophy.

PALMER, Philadelphia.

FAMILIAL PERIODIC PARALYSIS. J. MACDONALD HOLMES, Brit. M. J. **1**:80 (Jan. 18) 1941.

Familial periodic paralysis is characterized by sudden attacks of flaccid paralysis in one or more muscle groups; it is usually symmetric and occurs most often in the limbs. The paralysis can be produced by the oral administration of large quantities of dextrose. The serum-potassium level is abnormally low during an attack. Although the mechanism of the cause of the attacks remains inexplicable, Holmes believes that the available evidence suggests that an abnormal metabolic process in the muscle fibers is responsible and that the disturbance is not due to any central factor in the nervous system.

Two cases of the disease in brothers are recorded. In the first case large doses of dextrose induced an attack, during which the serum-potassium level was low. On oral administration of potassium salts, the paralysis rapidly disappeared and the serum-potassium level rose. Although the history in the second case was suggestive of familial periodic paralysis, the attack could not be induced by dextrose, dextrose and insulin or epinephrine.

ECHOLS, New Orleans.

EXPERIMENTAL STUDIES ON ALIMENTARY MUSCULAR DYSTROPHY. M. EKBLAD and G. WOHLFART, Ztschr. f. d. ges. Neurol. u. Psychiat. **168**:144 (Jan.) 1940.

Ekblad and Wohlfart produced muscular dystrophy in 15 guinea pigs, 2 and 3 weeks old. Diet 11 of Goettsch and Pappenheimer was used for two months,

without any significant effect. Enough vegetables, milk and lemon juice were added to make sure that vitamins B and C were not lacking. The same animals were fed diet 13 of Goettsch and Pappenheimer for the next two months. This diet is the same as diet 11 except that the food is treated so as to extract vitamin E. Flaccid paralyses developed in all the animals given this diet. Examination of the muscles showed atrophy such as is seen with disease of the anterior horns. Degenerative changes described by Pappenheimer were not found. The muscles of the lower limbs were especially involved. Similar, but less extensive, changes were found in the muscles of the trunk and upper extremities and even the head. There were some changes in the muscles, such as are seen in the dystrophies. Deposits of fat among the intact muscle bundles were observed in the more advanced stages of atrophy. The most striking finding was the degeneration of the cells of the spinal cord, especially in the lumbar region. The large motor cells of the anterior horns were especially affected. SAVITSKY, New York.

Special Senses

TONIC DEVIATIONS OF EYES PRODUCED BY MOVEMENTS OF HEAD; WITH SPECIAL REFERENCE TO OTOLITH REFLEXES: CLINICAL OBSERVATIONS. FRANK R. FORD and FRANK B. WALSH, Arch. Ophth. **23**:1274 (June) 1940.

It has long been known that movements of the head produce compensatory deviations of the eyes destined to preserve the orientation of the visual fields and to maintain visual fixation. These deviations depend on complex reflexes, some of them still imperfectly understood. The neural mechanisms lying in the cerebral cortex and neuraxis are concerned with the nuclei of the third, fourth and sixth nerves and their association tracts, with the controlling influences of certain supra-segmental structures.

The various mechanisms to be considered are the volitional movements of the eyes, optic fixation reflexes, labyrinthine reflexes, tonic neck reflexes and Bell's phenomenon.

Disturbances in the first of these mechanisms are produced by lesions in the cortex and in their projection pathways which cause paralysis of the various conjugate movements. Experimental and clinical investigations have shown that such reflexes arise in the retinas from visual stimuli, in the labyrinths from movements or changes in position of the head in space and in the muscles of the neck from changes in position of the head in reference to the body.

The optic fixation reflexes, also known as opticokinetic reflexes and psychooptical reflexes, have as their afferent pathway the optic radiation, with an efferent pathway from the occipital lobe back through the optic radiation and a segmental oculomotor apparatus. These are probably of greatest importance in diagnostic neuro-opthalmologic problems. They follow herewith:

1. If fixation is secured on a test object and the object is then moved slowly and at a uniform rate, the patient's eyes remain directed toward the object and may be drawn into any position desired. This is termed a following movement. The same phenomenon is elicited by the revolving drum.

2. If a linear series of letters or marks is placed before the patient, it is possible for the eyes to move from letter to letter along the line until a full range of movement is secured. This is usually impossible if the letters are not placed close together.

3. If fixation is secured on a test object and the patient's head is then rotated either actively or passively, the eyes will remain directed toward the object and in this manner may be carried into any position within the orbits desired. For example, if the eyes are fixed in the primary position on a test object and the head is then rotated about a vertical axis to the right, the eyes will be carried into the position of left lateral deviation by this maneuver. According to Holmes and Bielschowsky, when the movement of the head is performed slowly, this reaction is entirely due to optic fixation reflexes and is abolished if fixation is prevented.

4. When volitional movements of the eyes are weak but not lost, the fixation reflex may become dominant and the patient may be forced to interrupt fixation by jerking the head or blinking the eyelids before it is possible to move the eyes. Thus, it seems that loss of volitional movements of the eyes is associated with inability to inhibit fixation reflexes.

5. The loss of optic fixation reflexes alone results in disturbances of vision, for volitional movements are not entirely sufficient for normal fixation. The eyes seem to oscillate about the object of fixation and cannot be fastened on it for more than a moment. The symptoms are more severe when the test object is moving, when the head is in movement and when the test object is placed in the peripheral fields.

6. If a test object such as a light is presented in the peripheral fields, the eyes will sometimes move toward it. This is termed an attraction movement. The relation of this movement to the foregoing reactions is not clear. Bielschowsky expressed the belief that it is merely a fully developed optic fixation reflex but admitted that there is room for difference of opinion about this interpretation.

The labyrinthine reflexes either arise in the semicircular canal or the otolith apparatus. They are diagnostic of situations which occur in the labyrinth and in its relationship with the reflex pathways.

The tonic neck reflexes are compensatory and of the same nature as the otolith reflexes. They are best illustrated in the rotations of the vertical axis of the eye with respect to changes in the position of the head in its relation to the body.

It is probable that the reflex arc for Bell's phenomenon arises in the cortical areas wherein lid movements are represented, and not in the true ocular gyric centers.

SPAETH, Philadelphia.

STUDIES OF THE VISUAL FIELDS IN CONNECTION WITH TRYPARSAMIDE THERAPY. LYLE S. POWELL and HERSCHEL S. SMITH, Arch. Ophth. **24**:276 (Aug.) 1940.

Studies of the fields of vision in connection with administration of tryparsamide have been considered important in the treatment of syphilis of the central nervous system. Tryparsamide as a therapeutic agent should not be discredited, but there is no doubt, on the basis of the authors' controlled studies, that the promiscuous use of the drug should be strongly condemned. Tryparsamide, not unlike many other therapeutic agents, has a tonic and a toxic action. The tonic action is manifest in the visual fields by an expansion, which is usually transient. The expansion frequently is associated with improvement in the patient's physical and mental condition. The toxic action is shown by a constriction of the visual fields, which may occur during the first injections or may follow the initial expansion associated with the tonic effect.

Of the 16 patients studied, 11 showed a constriction of the visual fields, 3 no appreciable change in the fields and 5 an early expansion of the fields which was later followed by a constriction.

SPAETH, Philadelphia.

Diagnostic Methods

AN OBJECTIVE SIGN (GANS-RODIET) IN CHRONIC ALCOHOLISM. M. K. AMDUR and S. T. GINSBERG, Psychiatric Quart. **15**:42 (Jan.) 1941.

Amdur and Ginsberg describe a phenomenon consisting of hemianesthesia of the lateral half of both scleras said to be present temporarily in acute, and more permanently in chronic, alcoholism. The authors suggested that this phenomenon is the result of excretion of alcohol by the lacrimal gland and is due to a local toxic effect. Of 100 alcoholic patients, 62 showed a positive sign bilaterally. The sign was present in 15 of 200 patients without a history of alcoholism. Of these, 12 had anesthesia of the whole sclera and syphilis of the central nervous system. The sign is recommended as a test for alcoholism.

SIMON, Worcester, Mass.

Encephalography, Ventriculography, Roentgenography

THE DIAGNOSTIC SIGNIFICANCE OF CRANIAL ROENTGENOGRAMS IN PITUITARY DISEASE. M. A. GOLDZIEHER, Endocrinology **27**:185 (Aug.) 1940.

Peculiarities in the size and shape of the sella turcica and abnormalities of the clinoid processes are well known sources of information concerning lesions of the pituitary gland. Comparatively recent work on the structural deviations of the cranial bones and abnormal development of the sinuses and their relation to disease of the pituitary indicates that these abnormalities are also of importance in the diagnosis of pituitary disease.

Experimental evidence indicates that the development of the paranasal sinuses, together with the general pneumatization of the cranium, is dependent on the growth-promoting function of the anterior lobe of the pituitary. Studies of the growth of the facial cranium and the development of the paranasal sinuses and mastoid cells reveal definite inhibition in pituitary dwarfism and in pituitary infantilism. Conversely, excessive expansion of the cancellous bone and of the sinuses is noted in acromegaly, gigantism and other manifestations of hyperactivity of the anterior lobe of the pituitary. Inadequate function of the anterior lobe during adult life results in a progressive diffuse sclerosis of the cranial bones, either appearing in a previously normal skull or superimposed on an originally hypoplastic skull. This sclerosis is particularly marked in previously overexpanded cancellous bone tissue.

The diagnostic significance of the structural abnormalities of the cranium, such as lack of excessive pneumatization and sclerosis, is emphasized by the practically specific relation of these changes to disease of the pituitary. In a series of 500 consecutively studied cases of pituitary disease, cranial dysplasia was present in 96 per cent, whereas in the control group in which clinical evidence of pituitary disease was absent minor changes were noted in only 9 per cent.

PALMER, Philadelphia.

MYELOGRAPHIC DIAGNOSIS OF SPINAL FRACTURES. A. JIANU and T. FIRICA, Rev. de chir., Bucaresti **43**:305 (May-June) 1940.

Jianu and Firica discuss the technic of roentgen examination of the spine after intraspinal injection of iodized poppyseed oil and the diagnostic value of the procedure in cases of fractures of the spine with nervous symptoms from compression of the cord or the nerve roots. Fractures of this type are frequently associated with posterior herniation of the nucleus pulposus of the intervertebral disks, thickening and calcification of the lateral ligaments and minute displacements of bony fragments which produce compression of nerve tissue but fail to show in an ordinary roentgenogram. Myelographic study is indicated after failure of early orthopedic treatment. Early myelographic examination is both useless and dangerous. Iodized poppyseed oil is injected in amounts of 4 or 5 cc. at the level of the lesion suspected or suggested by slight deformity of the vertebra in a plain roentgenogram. Smaller amounts of oil may fail to show partial block of the oil at the seat of the compressing lesion. After intrathecal injection of iodized oil, roentgenograms are taken when the patient is in the dorsoventral and the ventrodorsal position, and right and left lateral films when he is in the prone and the upright position. They are taken at a distance of 150 or 200 cm. between the plate and the anticathode. Anteroposterior and right and left lateral myelograms taken with the patient in the dorsoventral position are of great diagnostic value. They show clearly the partial blocking, even if moderate, at the seat of the lesion. A myelographic diagnosis of the abnormality is an indication for surgical intervention. In the case reported by the authors a myelogram demonstrated a fracture of the fifth lumbar vertebra with compression of the spinal cord by posterior herniation of the nucleus pulposus of the intervertebral disk.

J. A. M. A.

Congenital Anomalies

MEGACOLON (HIRSCHSPRUNG'S DISEASE) ASSOCIATED WITH CHANGES IN FUNDUS OCULI AND HYDROCEPHALUS. C. WORSTER-DROUGHT and J. SHAFAR, Brit. J. Child. Dis. **37**:153 (July-Sept.) 1940.

Worster-Drought and Shafar report a case of Hirschsprung's disease associated with hydrocephalus and optic atrophy. The somewhat obese blind boy, aged 8 years, was born prematurely of apparently normal parents and seemed to be of normal intelligence. He had suffered from obstipation since birth and for the last two years showed abdominal distention, with vomiting and diarrhea during the last year. Fecal discharges occurred every four days and were hard and bulky. A barium sulfate enema disclosed enormous generalized dilatation of the colon. The encephalogram revealed symmetric hydrocephalus. The optic fundi presented the picture of advanced bilateral optic atrophy, with vision of the right eye reduced to the mere perception of finger movements and with visual acuity of the left eye 6/60. The authors, discussing the cause and pathogenesis of the combined lesions, point out that in Hirschsprung's disease the hypertrophy cannot be accounted for by organic obstruction. The present tendency is to regard megacolon as a neuromuscular dysfunction due to an imbalance between the sympathetic and the parasympathetic division of the autonomic nervous system. What constitutes the exact nature of the imbalance is still disputed. In production of hydrocephalus three mechanisms may be involved: (1) obstruction to the circulation of the cerebrospinal fluid, (2) defective absorption and (3) excessive secretion. Obstruction in the pathways of the cerebrospinal fluid is the commonest cause of congenital hydrocephalus and arises either from developmental abnormalities or from inflammatory processes or fibrosis, secondary to intracranial hemorrhages sustained intra partum. Defective absorption may arise from hypothetic infection involving the arachnoid villi or from maldevelopment of these structures. The cause of hypersecretion of cerebrospinal fluid by the choroid plexuses is still *sub judice*. Megacolon and hydrocephalus in the present case are assumed by the authors to have developed in utero. Hydrocephalus was, however, not progressive. Measurements of the circumference and diameter of the skull showed little variation from the normal. The underlying cause was either a temporary condition or a defect that admitted of compensation. Congenital optic atrophy was regarded by the authors as secondary to hydrocephalus. J. A. M. A.

FAMILIAL OCCURRENCE OF PRURITUS, URTICARIA AND PARESTHESIAS WITH HYPERKINESIS OF THE LOWER EXTREMITIES. J. C. MUSSIO-FOURNIER and F. RAWAK, Confinia neurol. **3**:110, 1940.

Mussio-Fournier and Rawak describe a syndrome found in 3 members of one family. The clinical manifestations are pruritus, urticaria and hyperkinesis of the lower extremities caused by paresthesias appearing during rest. While other members of the same family also show allergic reactions, the authors express the belief that the present symptoms are not specifically allergic but are secondary to heredodegeneration of the nervous system. DE JONG, Ann Arbor, Mich.

Society Transactions

ILLINOIS PSYCHIATRIC SOCIETY

CHARLES F. READ, M.D., *President, in the Chair*

Regular Meeting, Jan. 2, 1941

Metrazol Shock Therapy in the Presence of Generalized Osteoporosis: Report of a Case. DR. V. L. EVANS, Aurora, Ill.

In view of the recent mention in the literature of vertebral injuries during metrazol shock treatment (Polatin, P.; Friedman, M. M.; Harris, M. M., and Horwitz, W. A.: Vertebral Fractures Produced by Metrazol-Induced Convulsions in Treatment of Psychiatric Disorders, *J. A. M. A.* **112**:1684 [April 29] 1939. Bennett, B. T., Jr., and Fitzpatrick, C. P.: Fractures of the Spine Complicating Metrazol Therapy, *ibid.* **112**:2240-2244 [June 3] 1939), it was thought the following case report might be of interest.

REPORT OF A CASE

A woman aged 58 was admitted to Mercyville Sanitarium June 18, 1938. Since March 1938 she had been very depressed, felt she was possessed by the devil and had a number of self-accusatory delusions. She had a good fund of general knowledge and no gross memory defect. She was extremely agitated, wrung her hands and looked the picture of despair.

Physical examination revealed nothing significant except emaciation and the presence of rather marked kyphosis of the dorsal portion of the spine. The urinalysis, hemoglobin determination, erythrocyte and leukocyte counts and Kahn test of the blood all gave satisfactory results. A roentgenogram of the spine taken in August 1936 was said to have shown the presence of generalized osteoporosis.

A diagnosis of involutional melancholia was made, and the patient was started on estrogen therapy, 10,000 international units being given on alternate days. This was kept up for many weeks, without any noteworthy benefit. She was then given successively amphetamine (benzedrine) sulfate and powdered opium, without benefit. She continued to be hopeless and dejected, and her delusions persisted.

After considerable discussion with her family, it was decided to give the patient metrazol shock treatment. In view of the osteoporosis, she was given calcium and vitamin D supplements to her diet for several weeks before treatment with metrazol was started.

A roentgenogram of the spine taken on July 17, 1939 revealed osteoporosis and marked narrowing of the seventh, eighth, eleventh and twelfth dorsal vertebrae.

She was started on metrazol treatment on July 19, 1939. After three convulsions she complained of pain in her shoulders, and there was marked tenderness on motion. Roentgenograms taken on July 31 showed generalized osteoporosis of the bones of both shoulder girdles and a complete transverse fracture of the surgical neck of the left humerus. As the fragments were impacted, no treatment was instituted, and three months were allowed for healing to occur.

The patient then had eight more metrazol treatments, from Oct. 31 to Nov. 24, 1939. There were six convulsions and two partial reactions. The patient became bright and cheerful, her delusions disappeared and she gained weight and slept well. Roentgenograms were again taken of the spine after the metrazol treatment had been finished, with no appreciable change in the appearance of the vertebrae. The patient returned to her occupation of teaching school and stated she felt as she did several years ago.

No mechanical measures were used to prevent vertebral injury. Only gentle pressure was exerted on the sternal area with the hand at the onset of the convulsions to check the initial forward lunge that occurs. The fracture of the

humerus was apparently due to straight muscle pull against the partially decalcified bone, and telescoping of the shaft of the bone resulted. Fortunately, this did not recur when the treatment was resumed after healing had occurred.

Comment.—The metrazol treatment was started in this case with many misgivings and much apprehension, because of the known osteoporosis and crushing of the vertebral bodies and the emaciation and general poor condition of the patient. However, after a year's trial of conservative measures no progress had been made, so that more drastic means were considered justifiable. The results were most gratifying.

Some might consider this treatment to border on the heroic, but I do not feel so. My thought is rather that if one has any belief in the efficacy of the treatment, one should permit its benefits to be had by patients who are bad physical risks, as well as those whose condition is good.

Mental Symptoms Following Surgical Procedures. Dr. Joseph Pessin, Madison, Wis.

Eleven female surgical patients who had had a total of 80 operations were studied from a psychiatric viewpoint. An attempt was made to determine the role of environmental and psychologic factors and unconscious motives which lead patients to undergo multiple operations. The number of operations per patient ranged from 4 to 11, with an average of 7 plus.

Nine patients were neurotic. In this group the significant environmental factors were an unstable home in early childhood, strict parents and marital failure. The chief psychiatric symptoms were recurring somatic complaints over many years, periods of despondency and suicidal attempts or fantasies. Two patients had acute depressive psychoses, which in each case followed multiple operations.

Some of the unconscious motives noted in the cases studied were an effort to avert mental illness, an attempt to escape from intolerable situations and a wish for death.

DISCUSSION

Dr. H. W. Brosin, Chicago: I have enjoyed Dr. Pessin's analysis of the psychologic motives which predispose patients to multiple operations. Members of the medical profession can learn much from such a study in which persons who present the depressive character or the self-damaging personality pattern are scrutinized from a psychiatric angle before surgical treatment is recommended. I am, of course, referring to those circumstances in which operation is elective and in which the organic indications are ambiguous or slight. The general practitioner can learn to recognize the various grades of depression, including those in which the patient betrays his depressive tendency by his behavior pattern rather than by a definitely depressed mood. Such "masked depressions" are often found in persons with compulsive characters, the overly conscientious or overly anxious, the migraine sufferers, the chronic ne'er-do-wells and persons with numerous somatic complaints. Sometimes one sees tendencies to a strong element of impulsivity, or even violence, which can be detected in the history in the form of irritability, with "acting out" of aggressive impulses, accidents of all kinds, including occupational and household mishaps, quarrels, recrimination, resentment and bitterness toward others. If the physician has time, he can verify the presence of these personality traits in the developmental history, as Dr. Pessin did in his series.

In a similar series which I reported at the western meetings of the American College of Surgeons in 1936, the central theme was the presence of the depressive character. Strong sadomasochistic trends were the rule, with obvious need for punishment. Many self-damaging or suicidal trends were present, as in Dr. Pessin's series. In fact, 1 of the patients that I wanted to present as an excellent example of good recovery for nine months hanged herself on the morning she was to return to the hospital.

I concur in the view that the demand for operation may be a defense measure in an attempt to ward off a mental illness, but probably more important is the demand as an expression of the illness itself. Unfortunately, physicians often

offer the patient surgical treatment because of the patient's provocative attitude. Some patients literally beg for an operation as a means of inflicting punishment on themselves. This is most convincingly seen in those cases in which polysurgery becomes a methodic means of suicide, a subject which has been amply discussed by Dr. Karl Menninger. This type of surgery, like suicide, may be a means of aggression and revenge against others, including the physician and the family. Seldom mentioned is the clever way in which some patients can utilize the physician's anxiety or his aggresive trends to obtain the desired operation. Some of my patients wanted operation because they were imitating some one who had obtained genuine benefits, but these persons may have been of a neurotic character. Others sought operation as an escape from an intolerable situation or as concrete evidence of their need for added sympathy and attention. A few were able to elaborate their fantasies about the operation itself, revealing such trends as the desire to surrender the self completely through anesthesia, the wish to be overpowered and the desire for evisceration or exposure. It is probable that on further probing, especially when the patient desires a pelvic operation, many more such fantasies could be elicited.

In closing, I should like to ask Dr. Pessin if he found any evidence of "abdominal migraine" or "functional bowel distress" among his patients.

Dr. Joseph Pessin, Chicago: First, why were all the patients studied women? I have been interested in the problem of polysurgery for the last three years, and I have seen only one man who had many operations; unfortunately, I did not have an opportunity to study him. I might say that most of my work has been confined to the women's service, but I tried to find out something about the men in the hospital who have had many operations.

In reply to Dr. Brosin's question in regard to evidence of "functional bowel distress": Does he mean gastrointestinal symptoms without organic lesions? Of course, patients undergoing gastroenterostomy and many patients with symptoms which led to operations for adhesions had numerous gastrointestinal complaints. All patients complained of one symptom after another.

A vicious cycle is set up in these patients. It seems as if such persons have an emotional conflict. Somatic symptoms which suggest a surgical syndrome appear; then an operation is performed, and the patient returns with more symptoms, some of which are referable to the organ that has been removed. In many instances the patient seems to feel resentful toward the physician for having performed the operation and haunts him with subsequent visits, more symptoms and new complaints.

I was not able to observe any effect of the shock of anesthesia in the patients studied.

By the question about justifiable operations did Dr. Brosin mean whether the patient had a pathologic condition? Many of the specimens that were examined did show lesions, but it is interesting that removal of the pathologic focus did not cure the patient; that is, the patient continued to have symptoms—not only symptoms referable to the organ that was removed but to other organs as well.

Meaning and Interpretation of Dreams. Dr. Meyer Solomon, Chicago.

Dreaming is a form of thinking during partial sleep or partial wakefulness and is mainly undirected, or fantasy, thinking, with varying levels between this and the other extreme of directed, or logical, thinking, the level depending on the degree of sleep or wakefulness.

Its chief characteristics, according to Hollingworth, are: (1) dissociation or a low level of integration, conscious activity and critical analysis, governed by the usual laws of association; (2) transformation of imagery type, especially from verbal and motor to visual and other forms; (3) substitution and confusion, sensory, perseverative and ideational; (4) superficial, uncontrolled associations, based on slight resemblances and trivial analogies and leading to phantasmagoric, bizarre pictures, metaphors, swift changes of scenes and incidents, dissolving views, fusions, mutations, reversals, etc., in time and space; (5) isolation of trains of thought;

(6) extreme suggestibility; (7) rapidly developing amnesia—a dream not narrated as it occurs is as difficult to report as a waking experience not narrated to oneself, since memory seems dependent on narrative or verbal associations at the time of the experience—and (8) redintegrative, perseverative patterns with substitutions, giving the appearance of symbolism.

Dreams frequently take the form of pictorial allegory or symbolic imagery because one regresses to a lower level of thinking, perceptual rather than ideational and mainly in visual images rather than words, especially words of abstract or general meaning. The higher functions of self-conscious reflection and control are not acting, and effective tendencies are freer and more uninhibited.

The psychology of much dreaming resembles that of childhood, yellow journalism, the funnies and many movies.

The content of dreams depends on the instigating stimuli and the total personality makeup. The personality makeup, past experiences and thoughts and perseverative and related patterns enter into the contents and play a role in interpreting and weaving into the dream the instigating stimuli of internal and external (psychologic and nonpsychologic) origin. Most dream material comes from or is associated with activities (incidents, thoughts, feelings, emotions) of the preceding day, especially the immediate presleeping state, because they were the last associations, with many cues.

As with wakeful thinking, the motivations and meanings of dreams are multiple: (1) thoughts and activities of the preceding twenty-four to forty-eight hours left uncompleted, abandoned, unsatisfied, unexpressed or repressed, with resurrection of old patterns, even from childhood; (2) trial apperception or interpretation, in dramatized form, of sensory impressions; (3) reproduction of past episodes, as in battle dreams; (4) mulling over events of the immediate past; (5) free intellectual play; (6) reviewing unsolved difficulties of adjustments in life; (7) problem solving —finding, or trying to find, a way out of a difficulty, and (8) desires, feelings, attitudes and emotions carried over from waking life into sleep and dreaming. Many dreams cannot be related to any definite experience by the dreamer.

Some dreams are of the greatest, others of the most trivial, personal significance. Dreams are normal and natural. The ordinary rules of learning, retention and reproduction should explain dream thinking, as well as wakeful thinking.

Dreams cannot be interpreted without other knowledge of the personality and experiences, past and present, of the dreamer. One may never know or recall the instigating stimuli, internal and external, during sleep, the experiences of the presleeping period and the recent and remote past. Dream study is often valuable for detecting indications of current attitudes, motivations, beliefs, adjustment problems and the like. Attempts at dream interpretation are a means or starting point for becoming friendly, chummy and confidential. Although there are reasons for everything in dreams, as in other thinking, one may not be able to find them in some, many or even most dreams.

Both dreaming and wakeful thinking are adjustment processes for relieving tension. An attempt at wishful fulfilment is present in many, though not necessarily in all, dreams, and when present need not be a veiled expression of suppressed desire.

If, as Hollingworth stated, by manifest content is meant the significance, symbol or idea and by latent content the signified, what the symbol stands for, or the meaning, then dreams and other thinking have the same so-called manifest and latent contents. Likewise, the principles of so-called dream work, the mental mechanisms of condensation and displacement, seem to be as common features of any act of memory as they are of dreaming.

Dreaming is a process of thinking, with symbols mixed or distorted, arising from irrelevant thought processes but derived in the same way as more rational waking thinking symbols, according to the usual laws of association. One must differentiate between an object, image, etc. (1) historically a symbol, which is true of every thought in dreaming or waking life, and (2) what it indicates symbolically at the moment to the individual in his personal life, which is not necessarily always characteristic of dream or wakeful thinking.

Although one is deeply indebted to all contributors to the understanding of dreams, especially Freud, there is no proof of the universal application of the dream theories of Freud, Adler, Jung, Stekel, Rivers, Watt and Horton.

In general, the psychologic activity in wakeful and sleeping states seems to be a reflection of the general life pattern—the personal experiences in the past, the interest and occupations in the present and the hopes and ambitions for the future. The psychologic processes in dreams are the natural result of multiple factors rather than of a single specific factor.

The views presented here may be classified as psychophysiologic, and are in harmony with the conclusions of Jackson, Hollingworth, Cason and others.

DISCUSSION

PROF. NATHANIEL KLEITMAN, Chicago: Dream interpretation from the scientific standpoint is still in its infancy. It depends on the report of the dreamer, which is entirely subjective. Dreamers may not recall what happened. Many psychologists and psychiatrists take issue with the dreamer. If he says that he does not dream, they insist he has forgotten that he dreamt. But all that is known about dreaming today comes from reports of the dreamers. Attempts to study dreams objectively have so far resulted in failure. It is known from laboratory observations that dreaming is often associated with a certain stage, or a certain depth, of sleep, but there is no definite electroencephalographic pattern characteristic of dreaming. Dreaming occurs in shallow sleep, or if it takes place in deep sleep, the dreamer does not remember having dreamt.

The progress that has been made consists essentially in comparing the dream events, as reported by the dreamer, with everyday happenings of conscious life, and an important characteristic of dreaming is the low type of analysis and integration. It is childish to a considerable extent. The dreamer meets a deceased relative, but that does not surprise him at all. It has been found in the laboratory with which I am associated that persons who have gone without sleep for three or four days may be dreaming while awake. Their so-called analyzing faculties are depressed, and they will start to answer a question that has not been asked, or they will continue a discussion that has not been initiated. As in dreaming, there are analysis and integration, but all cortical activity is crude.

Dr. Solomon mentioned so-called undirected thinking, or thinking without effort. I should like to call it by its usual name—the unconscious, with a capital U, meaning a mental process different from that one is aware of. The solution of some problems does not seem to require any effort. That sort of mental activity undoubtedly goes on in the waking state, in some persons at least, and expresses itself in hunches, inspirations, intuition, etc., but is considerably crowded out by conscious mental activity during the waking hours. In sleep, when the higher type of integration is absent, the unconscious, or the undirected, effortless solution of problems, as some like to call it, manifests itself more freely and may have a diagnostic significance. Dreams may thus help the psychiatrist in finding out what is wrong with the patient and may lead to successful treatment, but they do not tell much concerning the phenomenon of dreaming itself. In that respect the dream is much like the electrocardiogram. Without knowing much about the nature of its several waves, a cardiologist can tell what is wrong with a patient's heart by studying his electrocardiogram. Thus, successful empiric use of dreaming does not of itself constitute a solution of the dream riddle.

DR. JOHN FAVILL, Chicago: All know how easy it is for neurotic patients to exaggerate, to add and subtract to and to dress up and polish what they say, so that anything reported about somebody else is open to loose questions. It would be of value for every psychiatrist here to tell anything that he feels he knows about dreaming, however trivial it may seem. If I tell you something that I believe I know about dreaming, from my own experience, you can use your own judgment as to my sincerity. I think I know four or five things about dreaming; they may be of very small importance, but to me they are interesting. I often recall after a dream that something had flashed through my mind the day before

which obviously was the starting point of that dream, but only after it had flashed through my mind, without any thought of dreaming. If something goes through my mind and I think I'd like to dream about that, or I wish I could or I hope I don't, that completely blocks the process; I never dream of it. It is common experience, no doubt, with you as well as with me, but rather interesting, that perhaps twenty-four or forty-eight hours later some stimulus or some vague, unrelated happening makes me realize that either last night or the night before I had such and such a dream. It is therefore on file somewhere under the surface. That, as I say, is just a little thing I notice now and then and that I know is true with me.

Also, I have had, in periods of stress, with a difficult decision to make, a perfectly good freudian symbolic dream, which I am sure would be so labeled and interpreted by this audience, and yet it has been about the problem of which I had repressed nothing and for the solution of which I was using the very best of my efforts, with the realization, of course, of a definite conflict. That I cannot understand if I accept some psychoanalytic theories as true.

I shall end on a less serious note by saying that I practically never dream unless I eat a certain food the evening before, and practically always dream if I do eat it, and that is cheese.

DR. MEYER SOLOMON, Chicago: About Dr. Favill's symbolic dreams about problems, I suggest that they express simply a continuation of the attempt to solve an uncompleted problem and that with the low level of conscious integration the dreamer does the best he can and so the pictorial imagery enters into the picture and attempts to solve the problem that was not solved during the day. There is much symbolic imagery in dreams.

A Scale for Evaluation of the Prognosis of Schizophrenia. DR. PHYLLIS M. WITTMAN, Elgin, Ill.

Many empiric studies have been made in which schizophrenic patients who have improved have been compared with those who were unimproved in an attempt to determine the factors differentiating the two groups. These reports in general have shown a striking unanimity in the factors considered benign and malignant.

DISCUSSION

DR. CHARLES E. READ, Elgin, Ill.: The factors as they appear on the sheets are not evaluated solely on the basis of the history presented by the social worker. Of course, many appear as a result of the patient's trouble, and so are not entirely dependent on what the social service worker may report. I can vouch for the fact that the sources from which Dr. Wittman obtained her criteria of the process of schizophrenia are good ones—a formidable array of men who have published their work and are well known. Of course, the work of weighting various factors, as Dr. Wittman has said, is in the process of evolution. It is not contended, as I take it, that the weightings are final. For example, I might question the weighting on 17 neurotic tendencies. As a matter of fact, my associates and I see many so-called neurotic patients, at least we say they are psychoneurotic, as they first appear, and after they have been seen once or twice they are quite evidently schizophrenic. Possibly this rating is a little too favorable from the pathologic point of view. From my practical experience in staff conferences, in which we attempt to establish a prognosis and a treatment somewhat dependent on that prognosis, it seems to me that a procedure somewhat like this is worth while, since it is, as Dr. Wittman calls it, a rational approach, rather than an empiric evaluation.

DR. PHYLLIS M. WITTMAN, Elgin, Ill.: The chart shows the bimodal distribution. There are two peaks with a depression, or valley, in the center. Statistically speaking, a curve of that sort indicates that there are two types of cases included in the sampling that is used in the study; in this study it would appear that the

one group includes the cases in which the condition was diagnosed as schizophrenia and was of the schizophreniform type (the prognosis scores indicate that the prognosis was good) while the other group is made up of those cases of what is called "process" schizophrenia because the prognosis is poor (the patients do not improve whether they have shock therapy or not; the condition is definitely chronic).

DR. HUGH T. CARMICHAEL, Chicago: I notice that Dr. Wittman had to leave out 47 cases because the data were not sufficient. She has properly said her scale is not a test. It seems to me that there must be a much longer period of evaluation before one can draw any conclusion as to the efficacy of the material which she has introduced.

For this research, the results of 54 such empiric studies have been organized and combined into a weighted scale and used in a rational approach to a study of the prognosis of schizophrenia. Thirty factors (both malignant and benign) have been statistically weighted on the basis of their frequency and the importance ascribed to them in the experimental studies on which this scale is based.

The accuracy of the scale in predicting prognosis has been checked by follow-up studies on the 400 psychotic subjects whose scale results were used in the statistics for this report. The results indicate rather conclusively that: (1) The "prognosis scale" results are a better index in predicting improvement or the lack of improvement in schizophrenic patients than subjective generalizations based on "feeling" or "intuition," and (2) there is a somewhat bimodal distribution, with "process" schizophrenia grouped at one end of the continuum and recoverable "schizophreniform" psychoses near the other.

I personally rated all the cases used in the study; in addition, 61 of these were also rated by one of the medical members of the Elgin State Hospital staff. The correlation between the physician's ratings and mine were very close—a correlation of + 0.87.

I made the statement in my paper that the scale should be used only by the experienced psychiatrist or the abnormal psychologist, for I think that neither the average graduate in medicine nor the doctor of philosophy in psychology has had enough experience with patients with mental disease to evaluate these factors in the individual cases. It is a rating scale, not a standardized test, and hence is wholly dependent on the knowledge and experience of the rater in evaluating the factors.

The point Dr. Carmichael makes is a good one; that is, the value of the scale in a long term prognosis depends on a follow-up study of the case. However, the results I have collected so far demonstrate rather conclusively that with the scale one is able to predict with a high degree of reliability the short time prognosis, that is, to predict which patients will improve after shock therapy and which will not.

DR. L. B. SHAPIRO, Manteno, Ill.: I was much interested in hearing Dr. Wittman's presentation. I was acquainted with the work while it was being done. I was present when she first became interested in the subject. To me, it is interesting that research going on at present on the heterogeneous group of forms of dementia praecox has given results that cannot be properly evaluated. With the method reported it may be possible to break down this complex of dementia praecox into smaller and simpler complexes; perhaps it is with the employment of such a scale and with further elaboration and separation of the complexes of dementia praecox and its syndromes that research studies may make more relevant and more significant contributions.

DR. JULES MASSERMAN, Chicago: I should like to ask a question. I notice that Dr. Wittman stated that it takes a psychiatrist of experience or a specialist in abnormal psychology to utilize the test; under the circumstances I'd be interested to know how she rated each of the criteria.

DR. PHYLLIS M. WITTMAN, Elgin, Ill.: The evaluations were not just my own. The weights assigned the different factors making up the scale were deter-

mined on the basis of the frequency and importance ascribed to them as prognostic criteria in the 54 empiric studies of prognosis in schizophrenia on which the scale was based.

These empiric studies were retrospective in that they were made on schizophrenic subjects five or ten years after a diagnosis had been made, the patients were divided into a group showing improvement or remission and a group with chronic disease and the factors differentiating the two groups were determined. It was on the basis of these studies that I selected the factors for the scale. The weights assigned the factors were determined statistically.

CHARLES F. READ, M.D., *President, in the Chair*

Regular Meeting, March 6, 1941

Symptomatic Treatment of Hysteria. DR. PHILIP H. HEERSEMA, Rochester, Minn.

In discussions of therapy of psychoneurotic reactions, particularly hysteria, within the past decade, the analytic, or causal, approach has been predominant. Direct suggestion, persuasion, hypnosis and various forms of indirect, as well as direct, suggestion have been relegated more or less to the category of that which is practiced but rarely preached. This paper attempts to reintroduce the principles of direct suggestion in the treatment of certain types of conversion hysteria. A discussion of certain types of hysterical conversion, particularly in the older patient with the superficial hysterical structure, seems to indicate the justification for symptomatic treatment. Three cases are reported, with moving pictures demonstrating objective results to support this thesis.

DISCUSSION

DR. PHILIP HEERSEMA, Rochester, Minn.: Essentially, the physician's objective in symptomatic treatment of hysteria is to have the patient avoid the crutch of magical mechanisms or anything of a mysterious nature. It is simply a matter oftentimes of using faradic stimulation to prove to the patient, against his will, that function exists. In a recent case of monoplegia it was possible to demonstrate to the patient that he possessed perfectly good function by producing movement of his arm with this physical stimulation. The question of the secondary transfer of emotion, that is, after the physician has initially gained the patient's confidence, has been raised. I attempt to unload any acquired affective relation as quickly as possible after the initial rapport has been established by a diffusion of responsibility among others—the physical or the occupational therapeutist, for example. As a consequence there is no specific transference to or specific dependence on the physician himself. Another aim in this method is to keep the treatment as short as possible, without designating any period in which a person is going to be cured. If one is able to achieve this, the treatment of the patient is more satisfactory in terms of conservation of effort, which is the primary consideration of the therapeutist in the symptomatic approach.

Electroencephalographic and Clinical Studies Following Convulsive Shock Therapy of Affective Disorders. DR. NORMAN A. LEVY, DR. H. M. SEROTA and DR. ROY R. GRINKER, Chicago.

Electroencephalographic, neurologic and psychiatric examinations were carried out on 23 patients with affective disorders before and after the completion of convulsive shock therapy. Significant disturbances in the electrical activity of the brain were noted in approximately 50 per cent of the patients; these consisted of the development of 6 per second waves and, in the more severely affected patients,

of 3 and 4 per second waves of large amplitude, notched and dicrotic waves and suggestive spike and wave formations. Gross disturbances in intellectual functions of the "organic" type were observed in 45 per cent. The disturbances in the electric potentials, as well as in intellectual function, subsided in most instances in several weeks but persisted in some severely affected patients for many months, indicating that the disturbances in cerebral function following artificial convulsion therapy in therapeutic doses are for the most part reversible.

DISCUSSION

DR. NORMAN A. LEVY, Chicago: Dr. Grinker and Dr. Serota have previously shown that anxiety and tension affect the electroencephalographic curve. We do not feel that the convulsive shock itself had anything to do with the electroencephalographic disturbances, as the interval was great enough for the disturbance in electrical activity occurring during and immediately after the seizure to subside. Reports in the literature have indicated that this occurs during the same day. We ourselves have not made electroencephalograms during the acute phase, since other workers have reported such observations.

The disturbances following treatment are less severe if treatments are spaced more widely. In practical therapy we watch for the development of intellectual impairment and space the treatments accordingly. This is especially important in the treatment of patients whose intellectual capacities are of vital importance in their work and other activities. Ziskind (Memory Defects During Metrazol Therapy, ARCH. NEUROL. & PSYCHIAT. **45**:223 [Feb.] 1941) has shown that if the deficits following each treatment have not completely subsided by the time of the subsequent treatment an accumulation of residual deficits takes place.

DR. H. M. SEROTA, Chicago: With regard to sympathetic function, we have noted that blood pressures taken before treatment and thereafter, either daily or every other day, showed decreases as great as 40 to 50 mm. from the original level of 180 or 160 systolic and 90 diastolic. In some of our cases we noted much beta and delta activity prior to treatment. When treatment is over this may gradually be replaced by regular alpha activity. While it is quite possible that this may be considered "improvement," it must be remembered that what is measured over the various areas of the brain is an algebraic sum of cellular activity. It is conceivable that when an area under the electrode has been denervated a pathologic type of synchrony develops; I do not know whether this is pathologic, but from our studies of emotion I feel that this change from prominent beta to regular alpha activity may be primarily due to alleviation of severe emotional tension.

Speech as a Pattern of Behavior. DR. RALPH C. HAMILL, Chicago.

Learning of speech goes on throughout life. Enunciation and pronunciation are matters especially of the first five to ten years, when there is intensive learning of the body in all its uses and of standards of good and bad. Learning is put into words, and words carry a moral or esthetic value.

Acquisition of control of the speech mechanism gives great personal satisfaction. Speech is in words which must be as others expect. In childhood the conflict between self control and control by others may lead to disturbances of speech.

Children playing with words can expose knowledge of evil. Such exposure must be guarded against. Indefiniteness or indistinctness is useful in such self protecting —something that can be learned also. Stammering begun by chance may be continued by choice, become a habit and eventually be a complicated dysfunction of adult life.

The voluntary, conscious, purposeful elements in disturbances of speech furnish a pattern for the consideration of the various behavior disorders of childhood. These behavior disturbances lead to a feeling and reputation of wrongness: something that *should* be corrected. This "should" produces or increases the feeling of wrongness, which can pass to a psychoneurosis or a psychosis through the various

stages natural to mankind. Something done through choice proves wrong. This arouses anger at those who suggest one's being wrong. Such anger is wrong: It should be controlled. Such control *should* be possible; yet, again, there is the desire to behave as one wishes rather than as some one else has wished.

In a psychoneurosis, with its feeling of the need for self control, a further burden of apprehension arises out of the conflict between this need and the realization of the influence or control that others, and their conventions, exert. This is commonly expressed in such terms as "loss of self control," with various fears expressed as "I couldn't control my thoughts," "I must be losing my mind; I can't remember anything any more" and "Am I going crazy?" In a psychosis there is the feeling, often expressed in definite words, "I'm crazy; I'm not responsible." In the background is the "paranoid" idea that some one else "controls me."

The structure of the body leads to the type of function: Stimulation produces function according to structure—eyes and ears to see and hear, muscles to contract, vocal cords to sound, bladder to empty, etc. In the beginning this is reflex; however, the activity is felt, is sensed; memory is started; repetition and imitation follow; conscious control is attempted and encouraged both from within and by others. These others demand that this control should be as they say it should be.

This is especially true of speech. At first vocal noises are reflex. The noise maker hears the noises. Attention is directed to them. Throughout the first few years endless repetition leads to control that produces words. The words must be as others say they should be.

Herein lies much of the conflict; here are sources of anger and fear. Anger and fear are the natural parents of mental disease.

DISCUSSION

DR. CHARLES B. CONGDON, Chicago: It might be of interest to think in terms of the complexities of learning to speak and of language itself. I should like to mention the little word "and," which Dr. Hamill mentioned as being very simple. Prof. J. B. Rosser, of Cornell University, has recently shown how complicated it may become. If a three value logic is used in connection with the word "and," it is found to have 256 meanings. If a four value logic is used it acquires 14,348,907 separate and distinct meanings. If one applies this type of mathematical formulation to some of the more abstract words, one begins to realize the difficulties encountered in learning to speak the English language.

One of the factors that I have found interesting in dealing with speech difficulties in children is a "perfectionist drive" of a sort on the part of the parents. They believe that speech, being a unique human function, should be rendered with absolute perfection. Thus, a child who begins to say "ah-ah-ah" when he tries to get the proper word is immediately made to feel that something is wrong, and this idea is emphasized to such an extent in many cases that the child becomes a stammerer, probably as a defense against further indictment—at least he now has an alibi. Sometimes, simply through being shown that there is nothing essentially wrong about mistaking one word for another, the patient will manifest immediate improvement, which continues as long as the explanation is accepted, and he learns the language as he probably should have learned it in the first place, without overloading words either with "rightness" or "wrongness."

It is also interesting that among certain groups of people there is developed a rather specific type of lingo, patois or neologistic language. Among the crooks and hoodlums of Chicago, for instance, there is a lingo that is peculiar to the group; among homosexual persons there is a rather definite neologistic and euphemistic language; among college students of the present day there is a unique language, and so on. This phenomenon is something I do not completely understand, and I have sought in vain for an adequate explanation of it. Perhaps these unique languages serve some useful purpose in a way similar to that in which stammering serves the stammerer. The average "Betty Co-ed" of the present day speaks in terms that you and I would probably not understand at all if we were not made familiar with the particular meanings. An excellent article in a recent

issue of *Life* is entitled "Subdebese." A girl may speak of her boy friend as a "dope," a "lame brain" or "reprobate," and these may be terms of endearment. When she speaks of a boy as "my jewel" she means that she frankly detests him. In many cases there is an attempt made to avoid the dangerous words by resorting to euphemistic language, and so the young man in question is said to have considerable "B. U.," which, when translated, means "biologic urge." Most college girls want to avoid the word "sex," which has many dangerous connotations, so "B. U." becomes a substitute which, at the moment, is not contaminated. When it does become contaminated, the modern youth will easily find another substitute.

The symbols of obscenity which Dr. Hamill mentioned have an interesting history, and considerable research has been done in working out their development. Dr. Alvin W. Read, of the University of Chicago, told me that the word "to occupy," for example, was at one time considered the most obscene word in the English language. He also learned that for nearly five hundred years it did not appear in currently used dictionaries. Many have said that obscene symbols are used only by persons of the lower classes. This has been demonstrated to be false, for it has been found that persons in the so-called upper brackets of society are almost invariably familiar with the taboo words. It was interesting to note the reactions in this professional audience to Dr. Hamill's references to certain obscene symbols.

It is amusing to note that nearly every one who spoke here tonight, including the present speaker, has had some speech difficulty. One could say that every speaker so far this evening has stuttered or stammered and that if he heard similar efforts in his child's speaking he would be alarmed about the possible onset of stuttering. Dr. Wendell Johnson, of the University of Iowa, has stated that nearly all stutterers really begin to stutter when the diagnosis is made. He has found also that in the majority of cases the diagnosis is made by a person totally lacking in training to make such a diagnosis.

Dr. Hamill's mention of the obscene symbols interests me particularly because they almost always appear at some time during the process of training the stutterer to speak accurately. This presents a problem which is difficult to approach, and it taxes the ingenuity of the therapeutist to the utmost. The patient will often be found resorting to complicated means of evading the obscene subject, and usually only when one discovers and clarifies his evasiveness is one able to get therapeutic results.

Every psychiatrist should have the experience of trying to help a stutterer or stammerer. I find that not enough psychiatrists are interested in speech therapy. They prefer to leave the problem to the charlatans and the quacks.

CHICAGO NEUROLOGICAL SOCIETY

HARRY PASKIND, M.D., *President, in the Chair*

Regular Meeting, March 20, 1941

Distant Neuroanatomic Complications of Spinal Dysraphism (Spina Bifida): Arnold-Chiari Deformity, Hydrocephalus, Stenosis of the Aqueduct, etc. DR. BEN W. LICHTENSTEIN.

In a previous paper ("Spinal Dysraphism"; Spina Bifida and Myelodysplasia, ARCH. NEUROL. & PSYCHIAT. **44**:792 [Oct.] 1940) I emphasized that spina bifida is primarily an expression of inadequate or improper fusion of the tissues in the dorsomedian region of the developing embryo and the resultant pathologic states are therefore manifested in the cutaneous, mesodermal and/or neural derivatives of these tissues. Since to many the term spina bifida indicates a vertebral defect and since in many instances anomalies particularly neural in nature which belong to the spina bifida group of disorders occur without evidences of a bony

defect, the generic term spinal dysraphism was used to identify these conditions resulting from defective raphe formation.

In the earlier stages of human development the spinal cord extends to the lowermost portion of the sacrum and the spinal nerve roots pass horizontally, escaping through their respective intervertebral foramens. Since the growth of the spinal column is of greater magnitude than that of the spinal cord, changes in the topographic relation of these two structures soon occur. As the brain is more securely fixed to its surrounding structures than the spinal cord, a relative rostal migration of the latter occurs. This results in the final localization of the conus medullaris in the vicinity of the first or second lumbar vertebra, the caudal deviation of the spinal nerve roots becoming more marked as the lumbosacral portion of the spinal cord is reached, and in the development of the cauda equina.

In some cases of spinal dysraphism there is abnormal fixation of the spinal cord to the surrounding tissues, and this precludes its adequate rostral migration. This results in the following pleomorphic variety of neuroanatomic alterations: (1) a short cauda equina and a low-lying conus medullaris; (2) abnormal stretching of the spinal cord above the site of fixation; (3) elongation of the hindbrain, with localization of the medulla oblongata, the posterior medullary velum, the choroid plexus of the fourth ventricle and parts of the cerebellum in the vertebral canal; (4) dysplasia of some of the cerebellar folia; (5) elongation of the lowermost cranial nerves, with their compression at the foramen magnum by the impaction of the hindbrain; (6) stenosis of the aqueduct of Sylvius; (7) internal hydrocephalus, due to stenosis of the aqueduct of Sylvius and to the impaction of the hindbrain in the foramen magnum; (8) deformity of the medulla oblongata and of the posterior end of the fourth ventricle; (9) hydromyelia of the uppermost cervical segments of the spinal cord, and (10) pressure on the anterior spinal arteries and the vertebral system of veins at the foramen magnum.

DISCUSSION

Dr. Paul C. Bucy: This has been an interesting and instructive discussion of an intriguing subject. I have been particularly interested in the observations relative to the aqueduct of Sylvius. These, I believe, constitute a new contribution to the subject. I agree with Dr. Lichtenstein that actual atresia and obliteration of the aqueduct are seen in association with spina bifida and can be the cause of the hydrocephalus which so frequently exists in cases of this anomaly. However, in these cases of the Arnold-Chiari malformation I should place much less emphasis on the constriction of the aqueduct than Dr. Lichtenstein has done. It is difficult for me to believe that an opening, even though constricted, which is large enough to permit the free passage of air, as Dr. Lichtenstein stated, or of iodized poppyseed oil, as I showed before this society several years ago, could obstruct the flow of ventricular fluid sufficiently to cause hydrocephalus. All other evidence indicates rather that here one is dealing with a "communicating" hydrocephalus. Fluid passes freely from the ventricular system into the spinal subarachnoid spaces but is not able to enter the cerebral subarachnoid spaces, owing to the constriction and hyperplastic process in the meninges at the foramen magnum. This contention is supported by the morbid anatomic changes and by the fact that infection in the spinal subarachnoid space enters the ventricles but not the cerebral subarachnoid spaces and that air injected intraspinally ascends into the ventricles but not into the cerebral subarachnoid spaces.

At first glance it might appear that failure of the fourth ventricle to become dilated like the rest of the ventricular system favors the hypothesis that the obstruction lies in the aqueduct. It appears likely, however, that the pulling of the medulla oblongata and part of the cerebellum into the foramen magnum and upper cervical portion of the canal compresses the fourth ventricle so that dilatation is not possible. Furthermore, in cases of communicating hydrocephalus the fourth ventricle either does not dilate or does not dilate proportionate to the rest of the

ventricular system. The only instances in which there occurs marked dilatation of the fourth ventricle are those in which the obstruction lies at the outlet of the fourth ventricle, the foramens of Magendie and Luschka.

DR. ARTHUR WEIL: What is the cause of the connective tissue adhesions at the dorsal segments of the spinal cord, and at which embryonic month may this developmental disturbance have taken place?

DR. BEN W. LICHTENSTEIN: I am sorry that I cannot be in full agreement with Dr. Bucy. In any hydrodynamic system a slight narrowing of one of the passages may result in marked dilatation of the chambers in front of the stenosis. All are familiar with the extreme dilatation of the pelvis of the kidney, the ureter and the urinary bladder resulting from a mild obstruction to the urethra acting over a long period. I believe both the stenosis of the aqueduct of Sylvius and the Arnold-Chiari deformity result in the hydrocephalus present in some cases of spina bifida and that the importance of the former has not been sufficiently emphasized.

In answer to Dr. Weil, the abnormal fixation of the spinal cord to the connective tissue in the subcutis occurs most frequently in those cases in which mesodermal dysraphism is marked. The nonclosure of the vertebral arch is, as a rule, associated with nonclosure of the dura mater dorsal to the spinal cord (dural araphia). As a result, the spinal leptomeninges fuse with the neighboring tissue, which in many cases is the connective tissue of the subcutis. This fusion, I believe, takes place in the first few weeks of embryonic life, for the dysraphic defect frequently involves all three germ layers.

Influence of Thyroid and Sex Glands on the Chemical Constitution of the Brain. DR. ARTHUR WEIL.

This investigation is concerned mainly with a study of the various lipid fractions of the brains of white rats after removal of the thyroid and sex glands and of rats with hyperthyroidism. The method of the Macleans was used for the lipid studies and that of Fiske and Subbarrow for determination of phosphorus.

The outstanding features observed after feeding of thyroid powder to young rats were a decrease in body weight and an increase in the weight of the kidneys and heart. In the brain the acetone-soluble fraction was increased in weight and the alcohol-soluble one was decreased. There was an increase in the amount of phosphorus in the acetone extract and the residue of extraction, with mild diminution of the phospholipid phosphorus.

After extirpation of the thyroid there was retardation in growth of body, brain, kidneys and heart. The different lipid fractions and their phosphorus content were correspondingly reduced. In rats which had been partially thyroidectomized or in which an aberrant thyroid gland had undergone compensatory hypertrophy the effect was less marked. Qualitative studies showed that at least 25 per cent of the original gland has to be preserved in order partially to prevent the same effect as that produced by complete thyroidectomy.

Removal of the sex glands resulted in transformation of male and female rats into asexual, "intermediate" animals. Growth of body and brain was retarded in the male castrated rat, but was stimulated in the ovariectomized rat. Similar results were obtained with respect to the chemical constitution of the brain. In the castrated rat all the percentage deviations from the values for normal male rats were negative; in the ovariectomized rat they were positive. Qualitatively there were no marked differences between the brains of the four groups. However, the brain of the normal female rat contained a relatively higher amount of phosphorus in the alcoholic extracts, and the corresponding values for the brain of the spayed rat were diminished, though still higher than those for the male rats. The minus and the plus percentage deviations of the castrated and the ovariectomized rat indicate the influence of the removal of the internal secretion of the sex glands.

However, the figures for the two do not become identical, indicating, perhaps, the chromosomal influence of sex determination. The fact that the deviations of the values for the spayed rat from those for the normal female are relatively much higher than the deviations for the castrated rat from those for the normal male indicates that sex determination in the female rat is less stable than in the male.

Part of the material in this study has already been published (Phospholipids of Brain, Kidneys and Heart of White Rats in Experimental Hyperthyroidism, *Endocrinology* **21**:101 [Jan] 1937; Correlation of Sex and Chemical Composition of Central Nervous System, *ibid.* **29**:150 [July] 1941). The results of further investigations will appear in a later issue of the same journal.

Biopsies on the Brain Following Artificially Produced Convulsions. Dr. Gert Heilbrunn and Dr. Erich Liebert.

To study the effect of convulsive seizures on the brain, rabbits were subjected to artificially produced convulsions. Metrazol, picrotoxin, monobromidated camphor, thujone, insulin, nitrogen (by inhalation), air emboli and electric current were used as convulsive agents. The biopsy method was chosen for this study, because it allowed for examination of material of the same brain at various intervals after the seizure.

Pieces of brain substance were aspirated with a 16 gage needle. Specimens were taken two, five, ten, twenty, thirty, forty-five and sixty minutes after administration of the convulsive agent. Paraffin sections 4 or 5 microns in thickness were stained with cresyl violet. The operative procedure itself did not produce any demonstrable changes in the control animals.

The experiments were carried out on 36 grown rabbits. The alterations consisted chiefly in the loss of the sharp outline of the ganglion cells, disappearance of the Nissl bodies and swelling of the cells. The nuclei were eccentrically located, and vacuoles could be observed. The glial changes consisted chiefly in slight swelling of the astrocytes and oligodendrocytes. Alterations were first visible about five minutes after the administration of the convulsive agent, with the exception of picrotoxin. With this convulsant no changes were noted as long as twenty-five and forty-five minutes after the injection—until two seizures had occurred. All changes were qualitatively similar, regardless of the agent used. They differed, however, in acuteness of onset, in degree and in duration. The changes were more severe after electrically induced convulsions and least severe after injections of monobromidated camphor.

After thirty minutes the morphologic alterations decreased, and in many of the animals definite changes could not be demonstrated forty-five minutes after injection. If, however, a second or a third convulsion was produced, the fading of the morphologic changes was delayed and reintegration of the neuronal apparatus could not be observed during the experimental period.

Subconvulsive doses of the same drugs caused no significant difference in results. The alterations observed were attributed to a state of anoxia, as evidenced by the immediate changes following air embolism and, furthermore, by those following inhalation of nitrogen and those occurring during hypoglycemia. Direct toxic effect might also be considered as a contributory cause of the morphologic changes, since similar alterations were observed in animals treated with metrazol in which the convulsive movements were inhibited by curare.

DISCUSSION

Dr. Victor E. Gonda: It is important to know that artificially induced convulsions cause changes in the brain cells but that these changes are reversible. This substantiates the observations of Cerletti, in Italy, who also found that the changes with electrically induced convulsions are reversible. The authors state that they used in their experiments the plain alternating current, without converting it. It would be of interest that they use in their future experimental work the same

type of electric current that my associates and I are now employing in the treatment of human beings, namely, the sinusoidal current. Inasmuch as the results in treating mental disorders with this type of current compare favorably with those obtained with other types of convulsant therapy and the complications are less, it seems that the electric shock treatment will replace the other methods.

DR. LEWIS J. POLLOCK: I wish first to pay tribute to this report of excellent work.

The changes that have been described in these limited areas have been found to be reversible. Perhaps they are not pathologic at all, but functional.

I should like to discuss a point which was mentioned by Dr. Gonda, namely, that the current used by the authors was an alternating, and not a sinusoidal, one. This illustrates what I have long felt, that those who are using electric currents for the purpose of producing convulsions know little or nothing about electricity, and that if one is to use a potent agent of any type, physical or chemical, one should know all about it. It should hardly be necessary to call attention to the fact that alternating current obtained from a line is a pure sinusoidal current and that if, in the circuit used for treatment, a good transformer is used, there is little, if any, distortion of the wave form.

The fact that reversible changes have been described by Dr. Heilbrun and Dr. Liebert does not mean that other, irreversible changes are not produced. I believe that this measure should not be regarded as harmless until proved so by more extended experimental work. Certainly, the available literature on careful studies of the pathologic changes in the brain following electric shock indicates the possibility of considerable irreparable damage to the brain.

It is also of interest to note that petechial hemorrhage of the lungs occurs when animals, such as hogs, are shocked by an electric current preparatory to killing by bleeding.

DR. VICTOR E. GONDA: In answer to Dr. Pollock, the faradic and sinusoidal currents are both alternating currents, but, according to the experiments, the sinusoidal current causes less damage to the brain. I also think it is important that research workers should know more about electricity; still, the average physician doubtless can handle a standardized apparatus without being a physicist. If the treatment is of value, he will have good results, as a physician may have good results with the use of digitalis or metrazol without knowing exactly the chemical formula of these drugs.

The hogs of which Dr. Pollock speaks were killed after application of electric currents to their bodies. They might show different changes in their organs. So far we have had no opportunity to see changes in the lungs in patients treated with the sinusoidal current.

DR. A. J. ARIEFF: Dr. Heilbrunn mentioned the action of the convulsive drugs and electricity. I should like to know if they saw any animals in which unconsciousness occurred without tonic or clonic movements. If so, did they make any pathologic studies on these animals?

As to the current used, Dr. Heilbrunn said he did not have exact measurements because the instruments were not sufficiently accurate. In experimental electric convulsions produced in rabbits at Northwestern University Medical School, we have an apparatus so set up that with the aid of an oscilloscope the actual peak current can be determined. The maximum current with this apparatus did not exceed 100 milliamperes, probably ranging between 40 to 90 milliamperes even with an alternating current of 100 volts. This is probably the magnitude of the current used in the experiments of Dr. Heilbrunn and Dr. Liebert.

DR. GERT HEILBRUNN: I should like to thank Dr. Gonda, Dr. Pollock and Dr. Arieff for their interesting remarks. In reply to Dr. Gonda's question concerning the relatively high voltage and amperage used in producing electric convulsions, it was our purpose to keep them at the lowest possible limit. Yet convulsions

were not obtained with less than 80 or 90 volts, as measured with our instruments. We are quite aware that this voltage is relatively high when compared with that used in electric shock therapy of patients, and it is possible, therefore, that this might account for the fact that the specimens taken for biopsy showed no reversibility of alterations during the observation period of fifty to sixty minutes.

Dr. Arieff asked whether changes can be demonstrated in animals after passage of current without the production of myoclonic movements. I am unable to comment on that, since our so-called subconvulsive animals did have slight myoclonic twitchings.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

JAMES B. AYER, M.D., *Presiding*

Regular Meeting, March 20, 1941

Late Psychologic Implications of Early Injuries to the Central Nervous System. DR. BRONSON CROTHERS, DR. ELIZABETH LORD and MR. MANON MCGINNIS.

The 2 cases reported here illustrate the difficulties which face any one who attempts to predict the course of growth and development after encephalopathy in early childhood.

The first case is one of outspoken lead poisoning. The diagnosis was made at the age of 5 years, when frank polyneuritis was recognized, but the history makes it certain that the ingestion of lead occurred before the end of the second year. Careful psychologic studies revealed minimal evidence of disturbance of cerebral function at that time. Five years later slow progress in school and disturbing behavior led to careful reappraisal in the hospital. At that time irregularity of performance was striking. Appreciable, and presumably significant, quantities of lead were still present in the blood, though none had been evident in the bones two years before. A pneumoencephalogram showed no abnormality. Readjustment of the school program was followed by prompt and permanent disappearance of the social difficulties.

Now, after another five years, the child is an attractive, well adjusted person of almost 15 years, who is doing adequate work in the eighth grade. There is still lead in the blood. Whether this represents any threat is, of course, a question, but repeated spectroscopic estimations show a level at the very top of the normal range.

The second child was successfully treated for pneumococcic meningitis and subsequent abscess of the brain at the age of 1 year. Before the acute illness she is said to have had occasional convulsions, and these have been repeated at intervals since. They have not been a major source of difficulty.

From the structural point of view the repair of brain tissue is almost complete. There is slight asymmetry in position of the ventricles but no difference in size or shape.

The behavior of the child and her relation to her family and the community are far more significant than physical or psychologic data. At the age of 3 she was an obstinate runaway. She spent a few days in a state school, but her intelligence quotient, which was in the eighties, and the restlessness of the family resulted in her discharge. The family, with extraordinary patience, struggled along, often with the help of tolerant police, who retrieved the child when she strayed too far.

When she was 8 years of age, her family, in desperation, brought her for further study. At that time she showed definite irregularities, with defects of memory. Her mental status was obviously inadequate, with an intelligence quotient in the upper seventies. We were unable to teach her effectively.

The child is now 10 years old. Her family and the police are finding her behavior increasingly difficult. She appropriates babies of total strangers, takes them home and mothers them diligently. This habit is regarded with general disfavor, but she has, so far, escaped head-on collision with the courts.

The effect of the abscess on this child is, of course, not entirely clear, but the rest of the family, without great intellectual assets, have adjusted cheerfully, whereas our patient shows irregularities and loss of judgment which cannot be corrected. It seems probable that custodial care will eventually be mandatory.

DISCUSSION

DR. DOUGLAS THOM: Dr. Crothers' presentation is interesting and timely, since the pediatricians and the psychiatrists are getting closer together. A great many problems are psychiatric ones because they have been negected by pediatricians. I have always felt that mental hygiene should be reduced to such terms as can be utilized by pediatricians in everyday contact with children. Such physicians are in a position to follow up a good many problems that otherwise would be lost sight of. There are a large number of children who rate fairly high on the psychologic scale but who have marked defects of judgment which get them into difficulties.

DR. WILLIAM G. LENNOX: Has Dr. Crothers any other cases of gross encephalographic changes in which the patient has seemed to come back to normal?

DR. PAUL I. YAKOVLEV, Waverley, Mass.: I am impressed by one implication of this interesting paper. One often sees children with severe disturbances in their mental development following cerebral damage. Some of these youngsters eventually overcome their difficulties; others do not. The question arises: Is the eventual outcome purely a matter of the type and severity of the cerebral damage, or are there factors that must be operative to produce a favorable or an unfavorable outcome? I should like to ask Dr. Crothers whether his experience has led him to some opinion on the point.

DR. BRONSON CROTHERS: There are plenty of cases in which we have seen extraordinary restitution after dilatation and distortion of the ventricular system, sometimes with one side showing improvement and the other deterioration as encephalographic examination is repeated.

It is extremely difficult to answer Dr. Yakovlev briefly. One must consider (1) how much tissue is destroyed and (2) how much interference with growth there has been. In the one case the outlook was unfavorable from the start, with initial convulsions and a queer family. In the other case a relatively simple insult was present. In my opinion, in the case in which the child became feebleminded the structural condition and growth were more important than the constitution of the child.

Vascular Supply of the Striopallidum and Hypothalamus in Man. DR. LEO ALEXANDER and MR. JOSEPH M. FOLEY.

Vascular Supply of the Striopallidum.—1. The striatum (putamen and caudate nucleus), with the exception of the posteroventral, recurved part of the tail of the caudate nucleus and of the adjoining posteroventral crest of the putamen, receives its blood supply from the striate arterioles (striatocapsular arterioles). In two thirds of the cases the supply for the anteromedioventral tip of the head of the caudate nucleus and of the putamen is derived from the anterior cerebral artery and that for the remaining portion of the caudate nucleus and putamen from the middle cerebral artery. In one third of the cases all striate (striatocapsular) arterioles are derived from the middle cerebral artery. The posteroventral, recurved part of the tail of the caudate nucleus and the adjoining posteroventral crest of the putamen are usually supplied from the anterior choroidal artery.

2. The medial and intermediate segments of the globus pallidus receive their blood supply from the arteria chorioidea anterior (pallidohippocampocapsular artery), except in those rare cases in which this artery is vestigial.

3. The lateral segment of the globus pallidus, with the sole exception of its anteroventral tip, receives its blood supply from the anterior choroidal artery in one fourth of the cases and from the striate arterioles of the middle cerebral artery in another fourth of the cases; in one half of the cases its lateral part is supplied from the striate arterioles of the middle cerebral artery and its medial part from the arteria chorioidea anterior. The anteroventral tip of the lateral segment of the globus pallidus is supplied from the striate arterioles of the anterior cerebral artery in about two thirds of the cases and from those of the middle cerebral artery in one third of the cases.

4. There is always a sharp cleavage between the arteriocapillary bed supplied from the striate arterioles and that supplied from the anterior choroidal artery.

5. The "undivided length" (i. e., the length measured from the last source of abundant blood supply or from the last serviceable anastomosis to the terminal district) of the anterior choroidal artery is greater than that of any other cerebral artery of similar caliber. All other conditions being equal, this circumstance tends to predispose this artery to thrombosis under adverse general conditions favorable to clotting, such as circulatory disturbances and carbon monoxide poisoning.

6. The two most vulnerable structures of the human brain, the globus pallidus and the cornu ammonis, are both supplied by the anterior choroidal artery. The globus pallidus is supplied by its most anterior, anteriorly recurved terminal branches; the cornu ammonis, by its most posteroventral terminal branches.

7. The anterior limb of the internal capsule, the portion which is dorsolaterally adjacent to the knee, and the dorsal part of the posterior limb of the internal capsule are supplied from the striate arterioles.

8. The ventral part of the posterior limb of the internal capsule and the retrolenticular part of the internal capsule are supplied from the anterior choroidal artery, except in those rare cases in which that artery is vestigial.

9. The knee of the internal capsule is always supplied by one or two small direct branches from the carotid artery.

10. The striopallidal veins drain into the galenian, as well as into the cavernous, venous system.

11. There is a great paucity of significant supracapillary anastomoses in the striatum, as well as in the pallidum.

12. The capillary bed of the striatum exceeds in density that of any part of the cerebral cortex. The capillary bed of the globus pallidus is less dense than that of any part of the cerebral cortex.

Vascular Supply of the Hypothalamus.—1. The anterior region of the hypothalamus, including the preoptic and suprachiasmic regions, receives its arterial blood supply from the branches of the anterior cerebral and the anterior communicating artery.

2. The midregion of the hypothalamus, including the anterior periventricular nuclear system, the paraventricular nucleus, the supraoptic nucleus, the ventromedial nucleus and the dorsomedial nucleus, receives its arterial blood supply from the internal carotid and the posterior communicating artery. In some cases some nuclei (especially the paraventricular nucleus) draw their blood supply from both these sources.

3. The posterior hypothalamic region, including the prepeduncular fossa, the medial and lateral mamillary nuclei and the nucleus intercalatus, receives its arterial supply from the posterior communicating artery and from the posterior cerebral artery.

4. The venous drainage of the hypothalamic region goes into a special venous circle at the base of the brain, not into the galenian system.

5. The capillarity of the hypothalamic region is extremely dense. As in other species, in which it has been described before, the vascular pattern is extremely dense in the supraoptic and the paraventricular nucleus. No significant difference in the quantitative vascularity of these two nuclei could be determined. The medial mamillary nucleus is also densely vascular, but less so than the supraoptic or the paraventricular nucleus.

DISCUSSION

DR. KNOX FINLEY: The excellent technic used is convincing in demonstrating the local arterial supply of the basal structures of the central nervous system. The partial injection method, as used by the authors, is without question much better than the total injection method in studying the distribution of individual vessels. The total injection method is superior in studying the capillary architecture. Dr. Alexander referred to the similar vulnerability of the globus pallidus and Sommer's sector. I have the impression that Sommer's sector is the more vulnerable region. Dr. Alexander demonstrated that all of the cornu ammonis is supplied by branches of the anterior choroidal artery. It is not quite clear, therefore, how he accounts for the special vulnerability of Sommer's sector as due to the length of the anterior choroidal artery, when this vessel supplies a region many times larger. Mr. Foley has stated that the paraventricular nucleus in man is supplied by more than one arterial branch. I have found this true also in the monkey. The authors point out that the capillary richness of the paraventricular nucleus and that of the supraoptic nucleus are about the same and refer to my own studies on the monkey, in which the capillary supply of the supraoptic nucleus was found to be greater than that of the paraventricular nucleus. This difference in the capillary supply of these two structures in the monkey is definite and can be seen without the aid of a microscope. One explanation for the difference in the capillary supply of these two nuclei in man and in the monkey may lie in the difference in the density of the nerve cells. In the monkey the density of the nerve cells is much greater in the supraoptic nucleus, which has the greater capillary supply. If the nerve cells of these two nuclei are of more or less equal density in man, the similar capillary density, as found by the authors, could be explained.

DR. JAMES B. AYER: My father was surprised to find the vascular supply of the basal ganglia so variable. The illustrations current at that time showed an enormous lenticulostriate artery—the "artery of cerebral hemorrhage of Charcot." Careful dissection showed that this vessel is not constant, although the idea to the contrary is still fixed in the minds of some neurologists. Dr. Alexander, using another technic, confirms the dissection of Duret and my father.

MR. JOSEPH M. FOLEY: In answer to Dr. Finley, it was our impression that the cellular density of the supraoptic and that of the paraventricular nucleus are about equal, but we have made no cell counts on these structures.

DR. LEO ALEXANDER: In regard to Dr. Finley's other question concerning the globus pallidus and the cornu ammonis: These structures are located at the extreme ends of the anterior and the posteroventral terminal ramifications, respectively, of the peculiarly long and thin anterior choroidal artery. The most vulnerable part within the globus pallidus is its extreme anteromediodorsal tip, which is supplied by the anteriormost extension of the ramifications of the pallidal branch of the anterior choroidal artery, while the most vulnerable part of the cornu ammonis is Sommer's sector, which is supplied by the longest and thinnest branches arising from the posteroventral (hippocampal) terminal branch of this artery.

I should like to say that the work of Dr. Ayer's father (published in the *Boston Medical & Surgical Journal,* now the *New England Journal of Medicine* (**156**:768-769, 1907; **160** (supp.):1-29 [May 6] 1909) is a masterpiece not only of anatomic investigation but of writing. It is instructively and delightfully written, and I recommend it for perusal by all members of this society.

A Quantitative Method of Evaluating the Effects of Treatment of Neuromuscular Disorders: Report of Its Application in Ten Cases of Progressive Muscular Dystrophy Treated with Vitamin E, as Compared with the Results of the Oral Use of Prostigmine Bromide in Ten Cases of Myasthenia Gravis. DR. ROBERT S. SCHWAB, DR. JOHN E. SKOGLAND and DR. JOSEPH S. BARR.

The conflicting reports on the success of the use of vitamin E in treatment of neuromuscular disorders suggested the need of a quantitative method of evaluating the results of such treatment. Such a method would enable different groups of investigators to compare their results with greater ease and accuracy.

Three criteria were selected as essential to this approach and were carefully followed in this investigation.

First Criterion.—A numerical scoring system with which various degrees of improvement may be graded was used. Simple numbers lend themselves to statistical and percentage analysis, are clear to others and are less likely to be overweighted by enthusiastic impressions of either the patient or the physician. During the last six years, Dr. Henry Viets and one of us (Dr. Schwab) have utilized such a scoring table in evaluating the changes occurring in the symptoms of myasthenia gravis under the dramatic effect of intramuscular administration of prostigmine methylsulfate. The same set of values was applied in the present investigation, as shown in the following tabulation, with estimates of the percentage of improvement.

		Percentage
0	No improvement	0- 5
1	Slight improvement	5- 20
2	Moderate improvement	20- 40
3	Considerable improvement	40- 70
4	Marked improvement	70-100

Such a five point scale is simple enough to fit into any clinical or laboratory evaluation and has been of use in a number of other studies.

Second Criterion.—By means of a second five point scale a corresponding number of distinct phases of the improvement can be broken down. I is the patient's subjective report after he has carefully been informed of the meaning of the values 0 to 4. In column II is the physician's objective report of the situation as a whole (0 to 4). III, IV and V are three detailed specific tests of the clinical or laboratory picture, each of which gives measurable results and is graded 0 to 4. These tests are more reliable and accurate if they can be made by different investigators, or at least interpreted by two or three persons, and the mean values agreed to. Thus, if the patient's subjective report and the objective, clinical and laboratory scores are all 4, the sum is 20 (100 per cent). Discrepancies between subjective and objective values show themselves at once. Poor or negative results stand out clearly in such a chart. Analyses of a case of myasthenia gravis and 1 of progressive muscular dystrophy are shown in table 1.

TABLE 1.—*Analysis of a Case of Myasthenia Gravis and a Case of Progressive Muscular Dystrophy*

Average Case	Patient's Subjective Report (I)	Physician's Objective Report (II)	Scores for Three Specific Objective Tests, (III, IV, V)			Total Score	Percentage of Improvement	Evaluation of Result
Myasthenia gravis	3	3	2	4	3	15	75	Good
Progressive muscular dystrophy	1	0	0	0	0	1	5	Poor

Third Criterion.—A relatively similar disease or symptom complex that has an accepted, successful specific treatment is selected as a control, and the results for a reasonable number of patients with this disease are served in the same manner. A comparison of the results for this control group with those for the first group will give an excellent idea of the true efficiency of the treatment under discussion.

In this investigation we chose patients with myasthenia gravis for the control group and obtained evaluations on 10 consecutive patients appearing at the clinic who had been under oral treatment with prostigmine bromide. For column 3 in table 2, "Improvement in Presenting Complaint," we chose ptosis; for column 4, fatigue of the adductor pollicis muscle as measured on the ergogram, and for column 5, changes in the electromyogram as recorded at the same time. The results for the first 5 patients only are shown in table 2. Those for the rest, being similar, are omitted.

Case 5 was selected as the one in which the result was poorest during the particular month in which these figures were obtained.

TABLE 2.—*Evaluation of Improvement of Five Patients with Myasthenia Gravis Treated with Prostigmine Bromide*

Case Number	Patient's Subjective Report	Physician's Objective Report	Improvement in Presenting Complaint	Ergogram	Electromyogram	Total Score	Percentage of Improvement
1	4	4	3	4	3	18	90
2	3	3	2	4	3	15	75
3	2	2	3	3	2	12	60
4	3	3	4	4	3	17	85
5	2	2	1	2	1	10	50

TABLE 3.—*Evaluation of Improvement of Five Patients with Progressive Muscular Dystrophy Treated with Vitamin E*

Case Number	Patient's Subjective Report	Physician's Objective Report	Muscle Examination	Ergogram	Electromyogram	Total Score	Percentage of Improvement
1	0	0	0	1	0	1	5
2	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0
4	1	0	0	0	0	1	5
5	0	0	0	0	0	0	0

For the progressive muscular dystrophy group we selected 10 proved cases from the files and set up the therapeutic trial as follows:

1. Each patient had a careful neurologic examination by one of us.

2. Each patient had a complete muscular examination by an orthopedic worker (Dr. Joseph Barr).

3. Each patient had an ergographic study of four different muscles—the right and the left adductor pollicis and the right and the left quadriceps femoris.

4. As each ergographic fatigue curve was obtained, synchronous electromyograms were obtained from these muscles on a Grass ink-writing oscillograph.

After a base line was obtained, the patients were placed on a daily dose of 240 mg. of concentrated natural vitamin E (E. R. Squibb & Sons). A month or two later all four tests were repeated and the drug changed to another brand (Winthrop Chemical Co., Inc.), the same dosage being continued. A third examination was made in another month or two and the patient placed under treatment with alpha tocopherol (Hoffmann-LaRoche, Inc.), 100 mg. daily.

A fourth, and final, examination was made at the end of this period of medication. The total study usually occupied four to six months for each patient. Results were tabulated and evaluated on the basis of 0 to 4 and the scores added to the patient's subjective rating. The results in the first 5 cases are shown in table 3. The results in the remaining 5 cases, which were similar, are omitted.

It is seen at once that in this group of patients there exists no evidence that the vitamin has beneficial effects. This is particularly clear when the results are contrasted with those for the 5 patients with myasthenia gravis while under treatment with prostigmine bromide.

DISCUSSION ON PAPERS BY DR. SCHWAB, DR. DOYLE AND DR. VIETS AND THEIR ASSOCIATES

DR. JAMES B. AYER: I was extremely pessimistic about the efficacy of vitamin E until a few days ago, and am still skeptical. However, I have just seen a patient with bulbar palsy who was observed six months ago by Dr. Hauptmann and treated with vitamin E. I can say that nasal regurgitation has stopped while the patient has been under vitamin E therapy. I offer this observation for what it is worth.

DR. ALEXANDRA ADLER: I wonder if one is justified in stating, on the basis of Dr. Schwab's material, that vitamin E is of no value in the treatment of muscular dystrophies. One can conclude that the patients did not improve, but 4 of the 5 patients did not get worse. Perhaps in these patients the disease was arrested, if not improved.

DR. BRONSON CROTHERS: Were all the patients studied by Dr. Schwab and his associates past the age of 17, and have they any interest in young patients?

DR. JOHN SKOGLAND: We are aware that our material is composed of persons over 17. Stone (Treatment of Muscular Dystrophies and Allied Conditions, *J. A. M. A.* **114**:2137-2191 [June 1] 1940) reported improvement in 3 children. We thought it best to use patients at our disposal for whom the diagnosis was definite. These patients had been in the clinic from three to five years. They had received other types of treatment, with no benefit, and their condition had not changed a great deal. We thought that this would be a fair test of whether vitamin E was effective in treatment of adults, but the question with respect to children is still open and the tests for them should be repeated. The case of a patient aged 3 who reported marked subjective improvement is recorded in the literature. I wonder how such a report was obtained.

DR. LEO ALEXANDER: At the Third International Neurological Congress, held in Copenhagen in 1939, we heard the first paper on this subject, by Dr. Larus Einarson, who studied vitamin E deficiency diseases in animals. He and Dr. Axel Ringstedt reported some suggestive improvement in patients suffering from amyotrophic lateral sclerosis. Dr. Israel Wechsler reinvestigated this problem on his return home and was gratified by good results in several cases. Negative results by other authors do not necessarily disprove the observations of Einarson, Ringstedt and Wechsler. Pathologically, there are two types of amyotrophic lateral sclerosis: One of them, the rarer type, is characterized by pure "abiotrophic," essentially reversible lesions; the other, more common, type is characterized by degenerative-necrotizing, essentially irreversible lesions. It may be that the patients who respond to vitamin treatment are those with the "abiotrophic" type of the disease, which is otherwise clinically indistinguishable from the nonresponsive type of degenerative-necrotizing lesions.

DR. JOSEPH J. MICHAELS: The rationale of vitamin E therapy was based on the assumption that it was primarily for neurologic disturbances in which lesions exist in the nerve tissue, the spinal cord or the nerve fibers. In the dystrophies the lesion is primarily in muscle. Is this not a different systemic disease, and therefore

can one compare the results on the same basis? I do not know of recent discoveries concerned with these diseases, but in the past nervous and muscular disorders were looked on as entirely different. One could think of treating parkinsonism, multiple sclerosis and alcoholism with vitamin E on a rational basis, but it is problematic whether one could expect the same results with muscular disorders.

DR. WILLIAM L. HOLT, Worcester, Mass.: In his large group of cases, Wechsler has included instances of marked asymmetry and of marked variations in symptoms from time to time, cases of so-called spontaneous improvement. Has he by so widening his basis of selection included cases not ordinarily considered as properly belonging under this disease (degeneration of nerve cells of unknown etiology)? Have the authors seen any cases in which spontaneous improvement occurred, such as Wechsler has reported in his patients?

DR. JAMES B. AYER: Improvement is rare under ordinary conditions. Symptoms usually progress without remission.

Vitamin Therapy of Diseases of the Neuromuscular Apparatus. DR. ARTHUR M. DOYLE, Kingston, Ontario, Canada, and DR. H. HOUSTON MERRITT.

This article was published in full in the April 1941 issue of the ARCHIVES, page 672.

Therapeutic Use of Vitamin E in Amyotrophic Lateral Sclerosis. DR. H. R. VIETS, DR. E. H. TROWBRIDGE JR., and DR. T. GUNDERSEN.

Beginning in April 1940 at the Massachusetts General Hospital, 11 patients with amyotrophic lateral sclerosis and 6 with progressive muscular atrophy have been treated intensively with vitamin E. At the beginning of the treatment concentrated wheat germ oil was used, but this was followed in May 1940 by alpha tocopherol acetate. The earlier doses were 5 to 10 mg., given three times a day. This dose was soon found insufficient and was gradually increased, so that at the beginning of January 1941 almost all patients were taking 200 to 300 mg. per day. In the last six or eight weeks the dose has been stepped up to 450 mg. a day. In addition, various other vitamins have been given, preferably thiamine hydrochloride. Moreover, 6 other patients with amyotrophic lateral sclerosis have been treated outside the hospital, with results similar to those observed in the hospital group.

Now, at the end of ten months, 5 of the 11 patients with amytrophic lateral sclerosis have died, 3 are worse and the condition of 3 is unchanged. Of the 6 patients with progressive muscular atrophy, 1 has died, 3 are worse and the condition of 2 is unchanged.

In the last few weeks 1 patient treated outside the hospital with a dose of 450 mg. of alpha tocopherol a day has shown slight, but definite, improvement in that the fibrillations formerly observed over the chest, back and upper portions of the arms are now minimal and are confined to the lower parts of the arms and the hands. The patient's strength, moreover, has slightly improved. The condition of another patient, who is receiving a similar large dose, is only slightly changed for the better. It can be said that the improvement does not exceed a maximum of 5 per cent. In a number of cases a record of the fibrillations of the muscles was taken in the form of an electromyogram. In no case was there a change in the myogram as the result of treatment.

In conclusion, it should be pointed out that the only result of therapy with vitamin E and thiamine hydrochloride observed was possible slight retardation of the normal progress of the disease. When the dose was raised to a level of 400 to 500 mg. of alpha tocopherol per day slight improvement was noticed in 1 case. Death, on the other hand, occurred in about the number of cases one would ordinarily expect over a ten month period with such a serious disease.

JAMES B. AYER, M.D., *Presiding*

Regular Meeting, April 24, 1941

Extensive Resections of the Premotor Cortex for Athetosis and Parkinsonian Tremor (Klemme's Operation). DR. JAMES C. WHITE.

Since Dr. Klemme's report before this society on Jan. 23, 1941 I have resected large portions of the premotor cortex according to his instructions in 2 cases. (A motion picture was shown to illustrate the type of tremor before operation, and the patients were then presented.)

CASE 1.—As a result of a birth injury, a 23 year old woman had suffered since infancy from severe athetoid movements of the right hand and foot. These slow, writhing movements had prevented walking and had rendered her hand useless. Unfortunately, her condition was further complicated by traumatic ulnar paralysis (she had fallen and cut the nerve in her right forearm) and by a previous anterior chordotomy. This operation had not diminished her involuntary movements and had left her with residual spasticity. The cortical ablation, which was performed seven weeks ago, was followed by paralysis of the right arm and leg and complete cessation of the writhing movements. Neither facial paralysis nor aphasia was noted, although the patient was less talkative for the first few days. Voluntary movement returned first in the fingers (in ten days), then in the elbow and shoulder (in four weeks) and in the hip and knee (in six weeks); now, after seven weeks, only the foot and ankle remain paralyzed. For the past three weeks the patient has noticed an occasional slight involuntary movement in which she extends her right elbow. This has not tended to increase and in no way resembles the continuous squirming movements from which she suffered before operation. The patient feels that if her present status remains unchanged she can be set down as 90 per cent improved. She is now able to use her right hand in ways that were formerly impossible, and she is beginning to walk with assistance.

CASE 2.—In a husky male, aged 23, a fine parkinsonian tremor of the left hand developed after an injury to his head in a football game. Ordinarily such a rapid, fine tremor of a single extremity would not require operative treatment, but the patient was a professional singer, and on the stage the tremor was exaggerated and embarrassed him to such an extent that he was totally incapacitated by it. Operation was performed only ten days ago, and paralysis from postoperative swelling of the motor strip has recovered so rapidly that shoulder and elbow movements have already returned. Until wrist and finger control has returned it will not be possible to evaluate the effect on the tremor.

COMMENT

Operation in both these cases was carried out with local anesthesia. Both patients were cooperative, so that it was possible to map out the motor cortex by thyratron stimulation and to mark its extent by small numbers the positions of which were recorded photographically. The resection was carried from the most anterior portion of the area from which motion could be elicited to a point halfway forward to the frontal pole. In order to reach the full depth of the convolutions the resection was carried to a depth of 2 cm., and in to the falx in the first case, in which the leg was involved as well as the arm. The amount of brain tissue excised in the 2 cases weighed 21.5 and 18 Gm., respectively. It is realized that both patients are demonstrated at too early a stage to justify final conclusions. In a single previous case in which I had resected the cortex only as far back as the large interconvolutional vein in front of the fissure of Rolando (thereby leaving a strip of cortex nearly 2 cm. in width), the tremor recurred synchronously with voluntary movement. I feel that success in the procedure depends on mapping the motor area with extreme accuracy and leaving the minimal amount necessary to preserve the power of voluntary movement—probably a strip

no wider than 5 to 8 mm. I am trying to determine this exact amount by photographing the cortex before and after the resection. An error of a few millimeters in either direction may mean either recurrence of tremor or severe paralysis, but if this error can be avoided the method promises striking relief in the cases of uncontrollable tremor of disease of the extrapyramidal tract.

Arnold-Chiari Syndrome: Report of a Case. DR. WILLIAM JASON MIXTER.

The Arnold-Chiari deformity, or syndrome, was described independently by Arnold and by Chiari, the former, I believe, in 1894 and the latter in 1895. Since then other cases have been added to the literature. The deformity consists in protrusion of a considerable portion of the cerebellum through the foramen magnum, so that it lies dorsal to the medulla and the upper cervical portion of the cord. In almost every case so far described the deformity has been associated with spina bifida or meningocele and hydrocephalus. For this reason it would seem that the cause of this deformity was associated with these lesions.

The case of Mr. T. M. is presented. The patient had been operated on in infancy for an occipital meningocele and had had a considerable amount of hydrocephalus for several months thereafter. He has a rather long, narrow head, has always been a little slow mentally and during the past few months has shown a good deal of mental confusion, so much so that he was confined to a sanatorium. He was recommended to the Massachusetts General Hospital by Dr. Bunker and Dr. Ives.

Study in the hospital revealed mild signs of involvement of the pyramidal tract and cerebellum, as well as the mental confusion already mentioned. Lumbar puncture showed a moderate increase in pressure and total protein content of the spinal fluid. A ventriculogram showed marked hydrocephalus. An encephalogram showed a deformity of the cisterna magna, with a mass protruding through what appeared to be a somewhat deformed foramen magnum. Operation revealed an Arnold-Chiari deformity, with a considerable portion of the left lobe of the cerebellum extending downward to the second cervical vertebra. Numerous adhesions containing good-sized blood vessels ran from this portion of the cerebellum to the upper cervical part of the cord. The fourth ventricle was opened with some difficulty and seemed to be normal. On account of the difficulty of removal of this portion of the cerebellum and the probability that the opening made into the fourth ventricle would close immediately, Torkildsen's procedure was carried out, a no. 6 catheter being placed through a burr hole in the right lateral ventricle; the other end of the catheter was then carried down through a groove made in the occipital bone and the lower end of the catheter placed in the cisterna magna just below the lower end of the protruded cerebellar tonsil.

The patient made a good convalescence, and his mental condition, as well as the abnormalities referable to the cerebellum and pyramidal tract, has improved definitely since the operation. It is too early to state whether this improvement will be permanent.

Roentgenograms demonstrate the protrusion of the mass through the foramen magnum, and photographs show the postoperative position of the catheter. (Two other cases of similar nature from the records of the Massachusetts General Hospital were also reported and roentgenograms shown.)

Herpes Zoster Oticus: Report of Two Cases. DR. EDWIN M. COLE.

The object of this presentation is to draw attention again to the relation of facial paralysis to herpes of the ear in certain cases and to report 2 cases of this condition, with pictures and lantern slides pertaining to 1 of them.

The condition was first described by Hunt (Herpetic Inflammation of the Geniculate Ganglion: A New Syndrome and Its Complications, *J. Nerv. & Ment. Dis.* **34**:73, 1937), who discussed the syndrome of herpetic inflammation of the geniculate ganglion. Since then, in several subsequent publications, particularly

in a summary of these observations (Geniculate Neuralgia, Neuralgia of the Nervus Facialis, ARCH. NEUROL. & PSYCHIAT. **37**:253 [Feb.] 1937), he demonstrated the distribution of sensory fibers of the facial nerve which have their origin in the geniculate ganglion. He showed that "the cutaneous field of the geniculate system . . . is the external auditory canal." He claimed that there "exists the greatest variation in these sensory filaments, which is in harmony with their vestigial nature. Somatic sensory fibers from the ganglia of the vagus and glossopharyngeal nerves are also distributed in the same area, so that the auricular branches of all three nerves, the seventh, the ninth and the tenth, are represented on the auricle in the geniculate zoster zone." Hunt also showed that sensory fibers from the geniculate ganglion pass to the posterior nasal and palatal mucous membranes, while other fibers supplying deep sensibility of the face were demonstrated, as well as the fibers of the chorda tympani nerve. In this report, then, I am particularly interested in the geniculate fibers traveling in the seventh nerve with a cutaneous distribution in the external auditory canal. In 1931 MacDonald and Taylor reported 8 cases of herpes zoster oticus. The report of my 2 cases follows.

CASE 1.—F. R., a widow aged 61, white, came to the outpatient department of the Massachusetts General Hospital on Nov. 5, 1940, because of paralysis of the left side of the face, of one week's duration. The onset of symptoms consisted of severe pain behind and in the left ear, followed a day later by paralysis of the left side of the face. She could not think of any injury or trauma to her face, though she volunteered the statement that that side of her head was exposed while driving her car. There was no deafness, vertigo, tinnitus or visual disturbance. Examination showed complete paralysis of the face and a swollen left ear. There were slight tenderness of the left parotid gland and possibly some inflammation of the opening of Stensen's duct on the left. The following day it was noted that there were blebs in the external auditory canal on the left. The vesicular eruption persisted for at least two weeks, during which time the pictures which are to be shown were taken. The pain remained very severe for some time, gradually subsiding as the vesicular eruption began to disappear. The facial paralysis remained unchanged, and the patient left this locality and my observation at the end of November. I have not seen her since.

CASE 2.—D. M., a single white man aged 22, was admitted on Feb. 15, 1941, complaining of paralysis of the left side of the face. One week before he had observed a pimple in his left ear, which was very painful and discharged a watery substance. Three days later the left side of his face became sore and stiff and several pimples appeared in the ear. The pain became more localized to the ear, and he was unable to move the left side of his face. There was no impairment of hearing, no vertigo and no disturbance of taste. Examination revealed complete paralysis of the left side of the face and several crusted lesions in the external auditory canal, which he said were the remains of the watery pimples he had had in his ear. One month later the patient reported by letter that the sores in the ear healed rapidly and that he recovered fully from the facial paralysis about one month after the onset.

Progressive External Ophthalmoplegia. DR. AUGUSTUS S. ROSE.

Slowly progressive ophthalmoplegia, with or without preservation of normal pupils, is known to exist in a number of morbid conditions, notably neurosyphilis, diabetes and exophthalmic goiter. The form described in the medical literature as "chronic progressive external ophthalmoplegia" is rare and is considered by some (Wilbrand and Saenger, 1900) as a separate clinical entity. However, von Graefe, in his original communication on the disorder, in 1878, called attention to the associated labioglossolaryngeal paralysis in some cases. Most of the recent textbooks of neurology agree that slowly developing paralysis of the extraocular muscles occurs as a superior form of progressive bulbar palsy. Ten cases of the disorder

have been collected from the clinic at the Massachusetts General Hospital. In these cases there was considerable variation in age of onset, rate of progression, family history and extent of involvement. In 4 cases the extraocular muscles only were involved; in 5 there was weakness or paralysis of other muscles, in addition to the ocular palsies, and in 1 case the condition had questionably been nonprogressive since childhood. In 1 case the disease was familial. In 7 of the 10 cases the spinal fluid was examined. In 5 of these the total protein content was above 50 mg. per hundred cubic centimeters. No other abnormalities were found in the laboratory or roentgenographic studies. The opinion is expressed that chronic progressive external ophthalmoplegia, as represented by these cases, is a degenerative process involving the motor cells of the nuclei of the brain stem, with variations in degree and extent of involvement.

Ménière's Syndrome: Report of Three Cases. Dr. Madelaine R. Brown.

Three patents who have suffered from deafness, tinnitus and acute attacks of vertigo and vomiting are shown. One, aged 63, has had recurrent otitis media since the age of 15, but no vertigo until four years ago. The other 2 patients, aged 51 and 52, are brothers whose nerve deafness and attacks of vertigo began eight years ago. All have benefited from treatment with potassium chloride. The first patient gave no family history of paroxysmal disease of the nervous system or of deafness. One of the brothers had migraine headaches in the teens and early twenties, while their mother also suffered from migraine.

Of the last 16 patients with Ménière's syndrome who have been interviewed with respect to the occurrence of paroxysmal diseases of the nervous system in their families, 9 stated that one parent had suffered from migraine headaches. Three had had sick headaches themselves. All but 1 of the 16 patients had nerve deafness and had one parent with early and severe deafness. Aside from the brothers, 1 patient stated that his father had had similar attacks of vertigo, and 1, that her brother had recently shown the same symptoms. Two patients, 1 of whom was the first one demonstrated, gave negative family histories. None gave a family history of epilepsy.

In conclusion, Ménière's syndrome and migraine occur not only in the same family but also in the same patient. From this series, Ménière's syndrome accompanied by perception deafness appears to be an inherited disorder.

The Dural Sac and Conus of Fourteen Human Embryos. Dr. Milton Korb and Dr. Charles A. McDonald, Providence, R. I.

Great progress has been made in the study and surgical treatment of distress and disorders of the lower part of the back. Our study was undertaken to add a bit to knowledge of the growth and development of the dural sac and conus. It is essentially a neuroembryologic investigation. Fourteen embryos of increasing age and size were studied. The youngest embryo was 2½ months old; the oldest was a full term baby. The crown-rump lengths of the embryos ranged from 62 to 350 mm.

In every one of the specimens the dural sac and conus were dissected out with the aid of a dissecting microscope and a binocular loupe. Each dissection was photographed, and each photograph was enlarged so that the distance between the pedicle of the fourth lumbar and the fifth sacral vertebra was the same in each picture. The study was limited to the growth of three structures: the dural sac, the conus and the lower spinal ganglia. This presentation was simplified by a diagram constructed from the silhouettes of the photographs of the embryos dissected.

Dural Sac.—The 2½ month embryo had a dural sac, and its tip was at the level of the first coccygeal vertebra. At 4½ months the tip of the dural sac was at the level of the third sacral vertebra.

Conus.—In the 2½ month embryo the conus was at the level of the first coccygeal vertebra; in the 4½ month embryo, at the fourth lumbar vertebra, and at birth, at the third lumbar vertebra.

Lower Spinal Ganglia.—In 13 of the embryos all the sacral ganglia were outside the dural sac. In the 80 mm. embryo the fifth sacral ganglion was outside the dura on one side and inside the dura on the other side. The coccygeal ganglia, on the other hand, were inside the dural sac in 13 embryos. In 1 embryo, the 73 mm., both coccygeal ganglia were outside the dural sac.

Trephine Biopsy of Tumors of the Brain. Dr. Jost J. Michelsen.

In spite of great advances in neurosurgery, little has been accomplished in regard to the management of malignant tumors of the brain. A patient with a benign tumor, such as meningioma, astrocytoma, oligodendroglioma and some others, has a fair chance of relief. No satisfactory method of treatment is available for glioblastoma multiforme. This destructive lesion grows and recurs rapidly, without demarcation. Yet even if the course suggests a malignant lesion, neurologists, as well as neurosurgeons, favor major surgical intervention as the method of choice. It is desired to give the patient a chance as long as the clinical type of diagnosis is not confirmed. In other words, the craniotomy is actually performed for diagnostic purposes only.

During the last few months I have tried to obtain this information by employment of a minor surgical procedure, which is called the trephine biopsy method. A burr hole is made in the area of the tumor and enlarged to about 1 inch (2.5 cm.) in diameter. The dura is opened. If nothing abnormal is found on the surface a needle exploration is carried out. Then punch biopsy specimens are taken from areas of abnormal resistance and examined in the neuropathologic laboratory.

In order to place the burr hole correctly, the lesion must be well localized by clinical or accessory clinical methods. Furthermore, one must be familiar with the representation of the different parts of the brain on the surface of the skull. There are several schemes which help to determine this correlation. In the scheme as devised by Krönlein seven lines are drawn. The first passes from the lower margin of the orbit through the upper border of the external acoustic meatus to the occiput. A second line parallel to the first runs through the upper margin of the orbit. There are three vertical lines from just behind the mastoid process, from the condyle of the mandible and from the middle of the zygomatic process, respectively. A line connecting points *b* and *a* (in the slide) represents the central sulcus. A line dividing this angle into halves indicates the sylvian fissure. (A slide was shown of one of the burr holes in the region of the angular gyrus in a patient from whom a punch biopsy specimen showed glioblastoma multiforme.)

At present a trephine biopsy is considered feasible in cases in which the history and the clinical course indicate a glioblastoma multiforme. A careful choice, however, was made of possible candidates for this procedure, and only 4 patients have so far been treated by this method. They all had a history of rapid progression of symptoms and a left-sided lesion, a combination of circumstances which makes every neurosurgeon hesitant as to the advisability of radical measures.

Three of these patients had a glioblastoma multiforme, confirmed histologically. Two were discharged from the hospital after a week or so for terminal care, without further surgical treatment. In the case of 1 patient the original clinical localization was wrong and the first trephine biopsy specimen taken from the temporal area revealed nothing significant. A bone flap was turned down, and the tumor was located in the frontal lobe by means of a needle and punch inserted through a small hole in the dura. The patient died of pneumonia on the tenth postoperative day.

The fourth patient showed no localizing signs. The ventriculographic examination and biopsy were performed on the same morning. He died suddenly in the afternoon. The punch biopsy showed astrocytoma. Postmortem examination revealed a large tumor involving the thalamus and basal ganglia, and I am prob-

ably correct in saying that this tumor, although benign histologically, was inoperable and malignant by virtue of its location. I had a patient with a similar situation who died suddenly, without any surgical procedure.

I do not need to say that the principle of this method is not new. Every neurosurgeon occasionally has encountered a tumor or cyst of the brain through a burr hole while making a ventriculogram. As early as 1904, Neisser and Pollack in Germany, reported their results with a method which they called "puncture of the brain." They performed it for localization chiefly. Very small needles were used. Somewhat later Pfeifer tried to determine the type of a lesion. The results were not satisfactory. Furthermore, the work of these investigators seemed to have little practical value, since at that time the chances for a patient with a tumor of the brain, whether benign or malignant, were bad. Today, under circumstances quite different, one may find that the application of their principle in the form of an improved method is of considerable value. After the malignant type of a brain tumor has been established beyond doubt by trephine biopsy, one still can decide whether or not to attempt major surgical intervention. Unless unusual circumstances prevail, the effort will hardly be justified. This attitude may seem defeatist, but actually it is not, for, admittedly, relief is temporary only, and a method better than anything so far available is needed to help these unfortunate patients effectively.

Subdural Abscess. Dr. Charles S. Kubik and Dr. Raymond D. Adams.

The clinical features and pathologic or surgical observations in 14 cases of subdural abscess are presented. The sources of infection were paranasal sinusitis, in 12 cases, otitis media, in 1 case, and bronchiectasis with metastatic infection, in 1 case. The symptoms conformed to a fairly definite pattern. In the cases in which abscess complicated sinusitis they consisted of an acute sinal infection, usually an exacerbation of chronic sinusitis; orbital swelling; pain or headache, at first localized, later becoming generalized and increasing in severity; rise in temperature, as a rule to 103 F., or higher; leukocytosis; stiffness of the neck; drowsiness, rapidly increasing to stupor and coma, and focal signs. The last appeared at about the same time as drowsiness or stupor. Hemiparesis or hemiplegia occurred in every case. Paralysis of contralateral deviation of the eyes nearly always developed, and aphasia was observed in most cases of left-sided abscess. Jacksonian seizures were fairly common.

Studies of Spinal Fluid.—The pressure, which was nearly always increased, ranged from normal to 350 mm. of fluid. Cell counts generally ranged from 150 to 600 per cubic millimeter, with polymorphonuclear leukocytes predominating, though in 1 case the count was 15 (lymphocytes) and in another 1,200 (95 per cent polymorphonuclear leukocytes). The sugar content of the spinal fluid was normal. Chlorides were slightly decreased in 2 cases and normal in 2. The total protein ranged from 49 to 186 mg. per hundred cubic centimeters. No organisms were found in smears or cultures.

Except for absence of sinal infection and orbital swelling, the clinical manifestations in the 2 other cases (of otitis and bronchiectasis) were similar to those complicating sinusitis. The course was rapidly progressive. In 12 cases death occurred six to twenty days after onset of headache and two to eight days after focal signs were first observed. In 2 cases recovery took place after drainage of the abscess through a frontoparietal craniotomy opening.

In a majority of the 12 cases in which autopsy was performed, extension to the subdural space took place by direct extension through the dura; in the remainder there was thrombophlebitis involving venous sinuses, usually the superior longitudinal. The subdural pus in all cases covered the greater part of the lateral surface of the hemisphere, with the greatest amount situated over the lateral aspect of the frontal lobe. It was not encapsulated, though in some of the cases of older abscesses there was organization of the exudate on the inner surface of the dura. There was regularly a localized subarachnoid exudate, conforming in its distribution to that of the subdural exudate, but scarcely any generalized meningitis. The

frontal lobe beneath the abscess was depressed, somewhat as with subdural hematoma, and in the underlying cortical gray matter there was severe ischemic necrosis, presumably secondary to thrombophlebitis of cerebral veins, which could be clearly demonstrated in some of the cases.

It was pointed out that the clinical picture in each case was similar and, this being so, that the diagnosis can be made in time to save some of the patients. Drainage, it was thought, should be through a lateral frontal craniotomy opening, and not through the frontal sinus or a mastoidectomy wound. Performed in this way, the operation is simple and quickly performed, and, if the results are negative, little or no harm is done, provided that the brain is not explored. Once the infection has reached the subdural space nothing is to be gained, and much may be lost, by operating on the sinuses or the mastoid. These may be taken care of later, if necessary, as was done in the 2 cases in which recovery took place.

PHILADELPHIA NEUROLOGICAL SOCIETY

BERNARD J. ALPERS, M.D., *Presiding*

Regular Meeting, March 28, 1941

The Physiologic Concept of Function of the Basal Ganglia. DR. JOHN F. FULTON, New Haven, Conn.

This survey of the two divisions of the extrapyramidal system leads to several general conclusions, as well as to a number of practical considerations, which may be summarized as follows:

1. Phasic movement is integrated by that part of the corticopontocerebellar system which passes to the neocerebellum. Destruction of the neocerebellum leads to tremors of action which are most conspicuous at the termination of volitional movements. Such action tremors disappear when the precentral convolution of the cortex is removed.

2. Postural adjustments are integrated by both systems, the corticostrionigral and that part of the corticopontocerebellar which joins with the paleocerebellum. The antigravity and equilibratory postures are adjusted by cortical mechanisms acting in association with the anterior and posterior lobes of the cerebellum, whereas the other, more complex, postural adjustments not having primarily to do with gravity or with the position of the body in space find integration through the corticostrionigral system.

The cerebral cortex thus becomes the common focus of integration of the extrapyramidal systems, both the division to the striatum and that to the cerebellum, and through thus coordinating the postural with the phasic mechanisms, absolute smoothness and precision of action are made possible. "Posture," it is said, "follows movement like a shadow," and this would be wholly impossible if the two were not integrated from a common level.

Other more practical considerations emerge from this concept of interaction of the postural and the phasic mechanisms, namely, the physiologic basis for surgical intervention in the corticostriatal syndromes, and possibly also in the corticocerebellar.

The work by Bucy and Buchanan (1932; see also Bucy, 1940), Putnam (1940), Meyer (1940) and, particularly, Klemme (1940) has focused attention on the possibility of relieving patients afflicted with severe parkinsonism, choreoathetosis, hemiballismus, etc., through a regional cortical ablation. Similarly, Aring and Fulton (1936) showed experimentally that severe cerebellar tremor could be abolished by precentral lesions, but, as far as I am aware, no one has

attempted to apply this clinically—possibly for a very good reason, namely, that the motor deficit would be worse than the tremor.

But in the case of severe hemichorea, and in certain cases of recalcitrant Parkinson tremors, conspicuous, and apparently enduring, relief has followed ablation of area 4 or of area 6 from the cerebral cortex on the side opposite the affected extremity. Klemme's operation involved making a large lesion in the premotor region, area 4 being left essentially intact. Bucy, on the other hand, has reported (1940) several excellent results from ablation of area 4 (involving only the posterior few millimeters of area 6). It is not possible at present to say which is the operation of choice. I feel certain that complete ablation of areas 4 and 6 will arrest a Parkinson tremor, hemiathetosis or chorea, as well as severe cerebellar tremor. Ablation of area 4 will produce much the same result, as far as cerebellar tremor is concerned, but there tends, with recovery of motor power, to be redevelopment of the cerebellar symptoms. This has likewise proved true in certain clinical cases of hemichorea, in which the symptoms have ultimately returned after small precentral lesions. From the physiologic standpoint, an ablation of area 4 is likely to be more effective than an ablation of area 6, but if, as Klemme maintains, a large ablation of area 6 gives symptomatic arrest for an indefinite period, in a majority of cases, it would be the operation of choice, since lesions of area 6 are accompanied by far less ultimate motor deficit than lesions of area 4.

This field of work is still in its experimental stages, and I believe that the solution can come only through further clinical experience. I am confident, however, that in cases of severe conditions the operation is entirely justifiable, and I sincerely hope that physiologically minded surgeons and neurologists will continue to encourage studies of this character, for they may bring relief in conditions which in years past have been regarded as entirely hopeless.

DISCUSSION

DR. SAMUEL B. HADDEN: In teaching, and even in discussing, disorders of motion one is inclined to speak of upper and lower motor neuron syndromes with an air of finality, as though the physiology of voluntary movement were very simple. However, I am sure all realize how complex voluntary movement really is. Dr. Fulton's work is extremely valuable in the clarity with which it is presented and in its helpfulness in demonstrating the role of various cortical areas to function of the basal ganglia.

DR. HELENA E. RIGGS: I have examined the brains in 21 cases of extrapyramidal disease (Parkinson syndrome, 11; chronic chorea, 10). In all these cases there have been degenerative changes in the premotor cortex, the dentate nucleus, the Purkinje cells and the cells of the inferior olive, as well as in the basal ganglia. The degenerative changes in these areas were not isolated or specific, but were part of the picture of widespread cerebral parenchymatous degeneration present in any case of chronic disease. However, the degeneration in the premotor cortex was more severe than in the pyramidal area, while the degeneration in the Purkinje and dentate cells was more marked than in the adjacent pontile nuclei and the olivary cells showed greater deterioration than the cells of the adjacent hypoglossal nucleus.

DR. ELI MARCOVITZ: Has any work in Dr. Fulton's animal experimentation thrown light on the differences in the pathogenesis of the states of hypertonus which are differentiated clinically as spasticity and rigidity?

DR. R. A. GROFF: I wish to commend Dr. Fulton on his excellent presentation, both for directness and for clarity. I have operated on several patients with athetosis. There comes to my mind the case of a patient who had unilateral athetosis of the left arm. I ablated area 6, after much difficulty in determining the premotor area. The results of this operation were not satisfactory. I then

performed the operation described by Putnam, and this quieted the movements considerably. In another case I performed the operation of extrapyramidal section as described by Putnam, with only moderate success. I should like to ask Dr. Fulton one question: "What do you think, from a physiologic standpoint, is the procedure of choice?" Extrapyramidal tract section is beset with difficulties in the danger of damaging the pyramidal tracts and causing motor weakness. The operation of ablation of area 6 is unattended, so far as I know, with complications. Yet is it a more sound physiologic procedure?

DR. JOHN FULTON: I appreciate Dr. Hadden's generous comments about the paper. With regard to the conventional distinction between the upper and the lower motor neuron syndrome, I heartily agree that the usual distinction is misleading, since the upper motor neuron paralysis may be completely flaccid or highly spastic, depending on which components of the upper motor neuron are interrupted. Generally speaking, lesions of the extrapyramidal, give spastic hyperkinetic pareses, whereas lesions of the corticospinal pathway itself give predominantly flaccid pareses.

I am much interested to learn that Dr. Riggs has found degenerative changes in the premotor area in cases of parkinsonism. It does not surprise me, but I think the fact should be made much more widely known, since the tendency in cases of parkinsonism and of the postencephalitic syndromes has been to emphasize only subcortical lesions.

In reply to Dr. Groff, I feel that if equally beneficial results can be obtained by cortical ablation this is the procedure of choice, since tract section in the cervical portion of the cord will, at best, always be a hazardous procedure. From the physiologic standpoint I believe that ablation of area 6 is a more sound procedure than tract section, for reasons already stated in the body of the paper.

With respect to Dr. Marcovitz's question: In monkeys, lesions of Marion Hines's strip area give rise to clearcut clinical spasticity with increase of tendon reflexes, lengthening and shortening reactions and a clasp knife type of resistance to passive manipulation.

When area 6 is alone removed, a "lead pipe" form of resistance is encountered, in which the extremity tends to remain in whatever position it is passively placed. The resistance is plastic in quality and of equal degree at all ranges of passive movement. This is characteristic of premotor release, and I am not certain whether a clinician would call it rigidity or plasticity. When areas 4 or 6 are both removed, a springy rigidity occurs, similar to that seen in human hemiplegia.

Book Reviews

Las neurosis èn la guerra. By Gregorio Bermann. Paper. Price not stated. Pp. 242 + index. Buenos Aires: Aniceto Lopez, 1941.

The author of this volume, who was formerly director of the Argentine Psychiatric Mission and of the neuropsychiatric service of Military Hospital no. 6 (Madrid), commandant in the medical corps of the republican army and titular professor of the faculty of medicine of Córdoba, Spain, joined the loyalist forces of Spain in 1937 and played a large part in organizing the neuropsychiatric service of that army.

The present book was written in the first place as a guide to his colleagues. It consists of several rather disconnected parts. The first chapter consists of an outline of the subject, as presented at a conference in Madrid in May 1937, made up largely of theoretic considerations and quotations from the literature. The discussion on the paper by several psychiatrists is included. In subsequent chapters the various psychoneurotic syndromes are discussed, in a manner which will seem familiar to those who have read volume X of "The Medical Department of the United States Army in the World War" and the more recent collection, "The Neuroses in War," edited by E. Miller (ARCH. NEUROL. & PSYCHIAT. **45**:400 [Feb.] 1941). Next comes a series of messages addressed in popular terms to the soldiers of the republican army, and finally a series of miscellaneous resolutions, circular letters, etc., more of local than of general interest.

The following features of the book are of most value: There is insistence on the importance of political morale in the prevention of neuroses. "It is essential not alone to realize the specific mission [of neuropsychiatry] within the medical department, but also to contribute to the spiritual health of the soldiers and elevate their morale, to remove undesirable elements from the service, toughen the unstable, inspire those who contemplate avoiding their duty, support the vacillating, strengthen the weak, resolve inner conflicts and unite the combatants in such a manner as to further their common ideals."

A fine sense of justice and sympathy for the neurotic soldier, and even for the malingerer, runs through the volume. The author has evidently read much and thought much about the problem of responsibility for psychogenic disorders and has achieved a unified and consistent conception of the boundaries of the various neuroses. The methods of treatment which he recommends are those familiar to readers of recent English and American publications: establishment of advance hospitals close to the front, use of hypnotics and rest for acute conditions, then psychiatric observation followed by intensive "persuasive" reeducation and, finally, carefully supervised reeducation before return to duty.

The references are excellent and include many in French, German and Spanish which are often overlooked.

Compendium of Regional Diagnosis in Lesions of the Brain and Spinal Cord. By R. Bing. First American translation by W. Haymaker; eleventh German edition. Price $5. Pp. 275 + index and 132 illustrations. St. Louis: C. V. Mosby Company, 1940.

It is like seeing the son of an old friend to encounter Bing's "Compendium" in a new English translation, easily available to students and practitioners. There is scarcely any book in the field of neurology that is so concise, clear and useful to the experienced and the inexperienced alike. The new translation preserves the forceful style of the original, and includes the old, rather crude, but clear drawings and the simple tables of levels of muscular innervation and of differential diagnosis.

The cross sections of the spinal cord and medulla have been made even more schematic than in the original. Some new plates of myelograms and encephalograms have been added.

In a book free of doctrines there is little to go out of date. One can, however, recognize a few paragraphs in which recent investigations have rendered the subject easier to grasp. Thus, the term "tonus" is still employed in this edition as if every one knew what it meant. The diagram of the fields resulting from a lesion of the optic tract, on page 232, show a "macular sparing," which is now recognized to be erroneous. It would not be difficult to pick out other minor anachronisms. For the audience to which the book is addressed, they impair its usefulness only slightly.

Orbital Tumors: Results Following the Transcranial Operative Attack. By Walter E. Dandy. Price $5. Pp. 164. New York: Oskar Piest, 1941.

This little book consists chiefly of a series of well illustrated histories of 31 cases of tumor involving the roof of the orbit and intracranial cavity. In the series, there were 9 cases of dural meningioma with hyperostosis of the skull, 5 of Schüller-Christian disease, 4 of glioma of the optic nerve, 2 each of pure osteoma and of dural tumor without hyperostosis and 1 each of the following types: inflammatory mass, pure fibroma, osteomatous cyst, spindle cell sarcoma, round cell sarcoma, bilateral dural meningioma of the optic sheath, sarcoma with hyperostosis, periosteal sarcoma and carcinoma.

Operation, usually through a unilateral frontal or frontotemporal approach, was performed in 24 cases, with the astonishingly low mortality of 1 death. There was substantial relief of symptoms in practically all cases, even though the tumor could not be removed.

The author has done a real service in recording the excellent operative results for this group of tumors. The case histories are concise but adequate, and the pathologic reports are satisfactory. It is somewhat curious that no cases of mucous cyst of the orbit or of malignant exophthalmos are included in the series. This is doubtless because they are not strictly tumors, although the differential diagnosis is often difficult.

Schizophrenia in Childhood. By Charles Bradley. Price $2.50. Pp. 152. New York: The Macmillan Company, 1941.

This little book tells the story of schizophrenia in childhood in rather simple fashion, but very completely. The review of the literature on this subject is especially thorough, and the reviewer knows of no other place where such a complete bibliography can be found. The book offers little original material, since the author reports only 5 cases of his own, but as a place to find references to what others have done it has definite value.